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0352 U.S. P.O.

UTILITY
PATENT APPLICATION
TRANSMITTAL

(Only for nonprovisional applications under 37 CFR § 1.53(b))

Attorney Docket No.

210121.427C16

First Inventor or Application Identifier

Jiangchun Xu

Title

COMPOSITIONS AND METHODS FOR THE THERAPY
AND DIAGNOSIS OF PROSTATE CANCER

Express Mail Label No.

EL615231109US

0352 U.S. P.O.

06/27/00

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO:

Box Patent Application
Assistant Commissioner for Patents
Washington, D.C. 202311. ☐ General Authorization Form & Fee Transmittal
(Submit an original and a duplicate for fee processing)2. ☒ Specification [Total Pages] **206**
(preferred arrangement set forth below)

- Descriptive Title of the Invention
- Cross References to Related Applications
- Statement Regarding Fed sponsored R & D
- Reference to Microfiche Appendix
- Background of the Invention

- Brief Summary of the Invention
- Brief Description of the Drawings (if filed)
- Detailed Description
- Claim(s)
- Abstract of the Disclosure

3. ☒ Drawing(s) (35 USC 113) [Total Sheets] **16**

4. Oath or Declaration [Total Pages]

- a. ☐ Newly executed (original or copy)
- b. ☐ Copy from a prior application (37 CFR 1.63(d))
(for continuation/divisional with Box 17 completed)
- i. ☐ **DELETION OF INVENTOR(S)**
Signed statement attached deleting
inventor(s) named in the prior application,
see 37 CFR 1.63(d)(2) and 1.33(b)

5. ☐ Incorporation By Reference (useable if box 4b is
checked) The entire disclosure of the prior application,
from which a copy of the oath or declaration is supplied
under Box 4b, is considered to be part of the disclosure of
the accompanying application and is hereby incorporated
by reference therein.6. ☐ Microfiche Computer Program (Appendix)7. Nucleotide and Amino Acid Sequence Submission
(if applicable, all necessary)

- a. ☒ Computer-Readable Copy
- b. ☒ Paper Copy (identical to computer copy)
- c. ☒ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. ☐ Assignment Papers (cover sheet & document(s))9. ☐ 37 CFR 3.73(b) Statement ☐ Power of Attorney
(when there is an assignee)10. ☐ English Translation Document (if applicable)11. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations12. ☐ Preliminary Amendment13. ☒ Return Receipt Postcard14. ☐ Small Entity Statement(s) ☐ Statement filed in prior application,
Status still proper and desired15. ☐ Certified Copy of Priority Document(s)
(if foreign priority is claimed)16. ☒ Other: Certificate of Express Mail

17. If a CONTINUING APPLICATION, check appropriate box and supply the requisite information below and in a preliminary amendment

☐ Continuation ☐ Divisional ☒ Continuation-In-Part (CIP) of prior Application No.: **09/593,793**
Prior application information: Examiner not assigned Group / Art Unit not assigned☐ Claims the benefit of Provisional Application No. _____

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Respectfully submitted,

TYPED or PRINTED NAME Jane E. R. PotterSIGNATURE Jane E. R. PotterREGISTRATION NO. 33,332Date June 27, 2000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT

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Filed : June 27, 2000

For : COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF PROSTATE CANCER

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Date : June 27, 2000

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Assistant Commissioner for Patents
Washington, DC 20231


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Respectfully submitted,

Seed Intellectual Property Law Group PLLC


Amber Straub/Jeanette West/Susan Johnson

Enclosures:

Postcard
Form PTO/SB/05
Specification, Claims, Abstract (206 pages)
16 Sheets of Drawings (Figures 1-12)
Sequence Listing (369 pages)
Declaration for Sequence Listing
Diskette for Sequence Listing

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COMPOSITIONS AND METHODS FOR THE THERAPY
AND DIAGNOSIS OF PROSTATE CANCER

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Patent Application
5 No. 09/593,793, filed June 13, 2000, which is a continuation-in-part of U.S. Patent
Application No. 09/_____, filed May 12, 2000, which is a continuation-in-part of U.S.
Patent Application No. 09/568,100, filed May 9, 2000, which is a continuation-in-part of
U.S. Patent Application No. 09/536,857, filed March 27, 2000, which is a continuation-in-
part of U. S. Patent Application No. 09/483,672, filed January 14, 2000, which is a
10 continuation-in-part of U.S. Patent Application No. 09/439,313, filed November 12, 1999,
which is a continuation-in-part of U.S. Patent Application No. 09/352,616, filed July 13,
1999, which is a continuation-in-part of U.S. Patent Application No. 09/288,946, filed
April 9, 1999, which is a continuation-in-part of U.S. Patent Application No. 09/232,149,
filed January 15, 1999, which is a continuation-in-part of U.S. Patent Application No.
15 09/159,812, filed September 23, 1998, which is a continuation-in-part of U.S. Patent
Application No. 09/115,453, filed July 14, 1998, which is a continuation-in-part of U.S.
Patent Application No. 09/030,607, filed February 25, 1998, which is a continuation-in-part
of U.S. Patent Application No. 09/020,956, filed February 9, 1998, which is a continuation-
in-part of U.S. Patent Application No. 08/904,804, filed August 1, 1997, which is a
20 continuation-in-part of U.S. Patent Application No. 08/806,099, filed February 25, 1997.

TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to therapy and diagnosis of cancer,
such as prostate cancer. The invention is more specifically related to polypeptides
comprising at least a portion of a prostate-specific protein, and to polynucleotides encoding
25 such polypeptides. Such polypeptides and polynucleotides may be used in compositions
for prevention and treatment of prostate cancer, and for the diagnosis and monitoring of
such cancers.

BACKGROUND OF THE INVENTION

Cancer is a significant health problem throughout the world. Although Cancer is a significant health problem throughout the world. Although advances have been made in detection and therapy of cancer, no vaccine or other universally successful method
5 for prevention or treatment is currently available. Current therapies, which are generally based on a combination of chemotherapy or surgery and radiation, continue to prove inadequate in many patients.

Prostate cancer is the most common form of cancer among males, with an estimated incidence of 30% in men over the age of 50. Overwhelming clinical evidence
10 shows that human prostate cancer has the propensity to metastasize to bone, and the disease appears to progress inevitably from androgen dependent to androgen refractory status, leading to increased patient mortality. This prevalent disease is currently the second leading cause of cancer death among men in the U.S.

In spite of considerable research into therapies for the disease, prostate
15 cancer remains difficult to treat. Commonly, treatment is based on surgery and/or radiation therapy, but these methods are ineffective in a significant percentage of cases. Two previously identified prostate specific proteins - prostate specific antigen (PSA) and prostatic acid phosphatase (PAP) - have limited therapeutic and diagnostic potential. For example, PSA levels do not always correlate well with the presence of prostate cancer,
20 being positive in a percentage of non-prostate cancer cases, including benign prostatic hyperplasia (BPH). Furthermore, PSA measurements correlate with prostate volume, and do not indicate the level of metastasis.

In spite of considerable research into therapies for these and other cancers, prostate cancer remains difficult to diagnose and treat effectively. Accordingly, there is a
25 need in the art for improved methods for detecting and treating such cancers. The present invention fulfills these needs and further provides other related advantages.

SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compositions and methods for the diagnosis and therapy of cancer, such as prostate cancer. In one aspect, the present invention provides polypeptides comprising at least a portion of a prostate-specific protein, or a variant thereof. Certain portions and other variants are immunogenic, such that the ability of the variant to react with antigen-specific antisera is not substantially diminished. Within certain embodiments, the polypeptide comprises a sequence that is encoded by a polynucleotide sequence selected from the group consisting of: (a) sequences recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777, 789, 817, 823 and 824; (b) variants of a sequence recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777, 789, 817, 823 and 824; and (c) complements of a sequence of (a) or (b). In specific embodiments, the polypeptides of the present invention comprise at least a portion of a tumor protein that includes an amino acid sequence selected from the group consisting of sequences recited in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 706-708, 775, 776, 778, 780, 781, 811, 814, 818, 826 and 827, and variants thereof.

The present invention further provides polynucleotides that encode a polypeptide as described above, or a portion thereof (such as a portion encoding at least 15 amino acid residues of a prostate-specific protein), expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, immunogenic compositions, or vaccines for prophylactic or therapeutic use are provided. Such

compositions comprise a polypeptide or polynucleotide as described above and an immunostimulant.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a prostate-specific protein; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, immunogenic compositions, or vaccines, are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) an immunostimulant.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins.

Within related aspects, pharmaceutical compositions comprising a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a physiologically acceptable carrier are provided.

Compositions are further provided, within other aspects, that comprise a fusion protein, or a polynucleotide encoding a fusion protein, in combination with an immunostimulant.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a composition as recited above. The patient may be afflicted with prostate cancer, in which case the methods provide treatment for the disease, or patient considered at risk for such a disease may be treated prophylactically.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a prostate-specific protein, wherein the step of

contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as
5 described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a prostate-specific protein, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polynucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide;
10 under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective
15 amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4⁺ and/or CD8⁺ T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of a prostate-specific protein; (ii) a polynucleotide encoding
20 such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for
25 determining the presence or absence of a cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody. The cancer may be prostate cancer.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of:

- 5 (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step
- 10 (b) and therefrom monitoring the progression of the cancer in the patient.

- The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate-specific protein; (b) detecting in the
- 15 sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one
 - 20 oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

- 25 In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate-specific protein; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample

obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as
 5 monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon
 reference to the following detailed description and attached drawings. All references
 10 disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

BRIEF DESCRIPTION OF THE DRAWINGS AND SEQUENCE IDENTIFIERS

Figure 1 illustrates the ability of T cells to kill fibroblasts expressing the
 representative prostate-specific polypeptide P502S, as compared to control fibroblasts. The
 15 percentage lysis is shown as a series of effector:target ratios, as indicated.

Figures 2A and 2B illustrate the ability of T cells to recognize cells
 expressing the representative prostate-specific polypeptide P502S. In each case, the
 number of γ -interferon spots is shown for different numbers of responders. In Figure 2A,
 data is presented for fibroblasts pulsed with the P2S-12 peptide, as compared to fibroblasts
 20 pulsed with a control E75 peptide. In Figure 2B, data is presented for fibroblasts
 expressing P502S, as compared to fibroblasts expressing HER-2/*neu*.

Figure 3 represents a peptide competition binding assay showing that the
 P1S#10 peptide, derived from P501S, binds HLA-A2. Peptide P1S#10 inhibits HLA-A2
 restricted presentation of fluM58 peptide to CTL clone D150M58 in TNF release bioassay.
 25 D150M58 CTL is specific for the HLA-A2 binding influenza matrix peptide fluM58.

Figure 4 illustrates the ability of T cell lines generated from P1S#10
 immunized mice to specifically lyse P1S#10-pulsed Jurkat A2Kb targets and P501S-

transduced Jurkat A2Kb targets, as compared to EGFP-transduced Jurkat A2Kb. The percent lysis is shown as a series of effector to target ratios, as indicated.

Figure 5 illustrates the ability of a T cell clone to recognize and specifically lyse Jurkat A2Kb cells expressing the representative prostate-specific polypeptide P501S, thereby demonstrating that the P1S#10 peptide may be a naturally processed epitope of the P501S polypeptide.

Figures 6A and 6B are graphs illustrating the specificity of a CD8⁺ cell line (3A-1) for a representative prostate-specific antigen (P501S). Figure 6A shows the results of a ⁵¹Cr release assay. The percent specific lysis is shown as a series of effector:target ratios, as indicated. Figure 6B shows the production of interferon-gamma by 3A-1 cells stimulated with autologous B-LCL transduced with P501S, at varying effector:target ratios as indicated.

Figure 7 is a Western blot showing the expression of P501S in baculovirus.

Figure 8 illustrates the results of epitope mapping studies on P501S.

Figure 9 is a schematic representation of the P501S protein showing the location of transmembrane domains and predicted intracellular and extracellular domains.

Figure 10 is a genomic map showing the location of the prostate genes P775P, P704P, B305D, P712P and P774P within the Cat Eye Syndrome region of chromosome 22q11.2

Figure 11 shows the results of an ELISA assay to determine the specificity of rabbit polyclonal antisera raised against P501S.

Figures 12A(1), 12A(2), 12A(3), and B are the full-length cDNA (SEQ ID NO:591) and predicted amino acid (SEQ ID NO:592) sequences, respectively, for the clone P788P.

SEQ ID NO: 1 is the determined cDNA sequence for F1-13
 SEQ ID NO: 2 is the determined 3' cDNA sequence for F1-12
 SEQ ID NO: 3 is the determined 5' cDNA sequence for F1-12
 SEQ ID NO: 4 is the determined 3' cDNA sequence for F1-16
 SEQ ID NO: 5 is the determined 3' cDNA sequence for H1-1

SEQ ID NO: 6 is the determined 3' cDNA sequence for H1-9
 SEQ ID NO: 7 is the determined 3' cDNA sequence for H1-4
 SEQ ID NO: 8 is the determined 3' cDNA sequence for J1-17
 SEQ ID NO: 9 is the determined 5' cDNA sequence for J1-17
 5 SEQ ID NO: 10 is the determined 3' cDNA sequence for L1-12
 SEQ ID NO: 11 is the determined 5' cDNA sequence for L1-12
 SEQ ID NO: 12 is the determined 3' cDNA sequence for N1-1862
 SEQ ID NO: 13 is the determined 5' cDNA sequence for N1-1862
 SEQ ID NO: 14 is the determined 3' cDNA sequence for J1-13
 10 SEQ ID NO: 15 is the determined 5' cDNA sequence for J1-13
 SEQ ID NO: 16 is the determined 3' cDNA sequence for J1-19
 SEQ ID NO: 17 is the determined 5' cDNA sequence for J1-19
 SEQ ID NO: 18 is the determined 3' cDNA sequence for J1-25
 SEQ ID NO: 19 is the determined 5' cDNA sequence for J1-25
 15 SEQ ID NO: 20 is the determined 5' cDNA sequence for J1-24
 SEQ ID NO: 21 is the determined 3' cDNA sequence for J1-24
 SEQ ID NO: 22 is the determined 5' cDNA sequence for K1-58
 SEQ ID NO: 23 is the determined 3' cDNA sequence for K1-58
 SEQ ID NO: 24 is the determined 5' cDNA sequence for K1-63
 20 SEQ ID NO: 25 is the determined 3' cDNA sequence for K1-63
 SEQ ID NO: 26 is the determined 5' cDNA sequence for L1-4
 SEQ ID NO: 27 is the determined 3' cDNA sequence for L1-4
 SEQ ID NO: 28 is the determined 5' cDNA sequence for L1-14
 SEQ ID NO: 29 is the determined 3' cDNA sequence for L1-14
 25 SEQ ID NO: 30 is the determined 3' cDNA sequence for J1-12
 SEQ ID NO: 31 is the determined 3' cDNA sequence for J1-16
 SEQ ID NO: 32 is the determined 3' cDNA sequence for J1-21
 SEQ ID NO: 33 is the determined 3' cDNA sequence for K1-48
 SEQ ID NO: 34 is the determined 3' cDNA sequence for K1-55

SEQ ID NO: 35 is the determined 3' cDNA sequence for L1-2
 SEQ ID NO: 36 is the determined 3' cDNA sequence for L1-6
 SEQ ID NO: 37 is the determined 3' cDNA sequence for N1-1858
 SEQ ID NO: 38 is the determined 3' cDNA sequence for N1-1860
 5 SEQ ID NO: 39 is the determined 3' cDNA sequence for N1-1861
 SEQ ID NO: 40 is the determined 3' cDNA sequence for N1-1864
 SEQ ID NO: 41 is the determined cDNA sequence for P5
 SEQ ID NO: 42 is the determined cDNA sequence for P8
 SEQ ID NO: 43 is the determined cDNA sequence for P9
 10 SEQ ID NO: 44 is the determined cDNA sequence for P18
 SEQ ID NO: 45 is the determined cDNA sequence for P20
 SEQ ID NO: 46 is the determined cDNA sequence for P29
 SEQ ID NO: 47 is the determined cDNA sequence for P30
 SEQ ID NO: 48 is the determined cDNA sequence for P34
 15 SEQ ID NO: 49 is the determined cDNA sequence for P36
 SEQ ID NO: 50 is the determined cDNA sequence for P38
 SEQ ID NO: 51 is the determined cDNA sequence for P39
 SEQ ID NO: 52 is the determined cDNA sequence for P42
 SEQ ID NO: 53 is the determined cDNA sequence for P47
 20 SEQ ID NO: 54 is the determined cDNA sequence for P49
 SEQ ID NO: 55 is the determined cDNA sequence for P50
 SEQ ID NO: 56 is the determined cDNA sequence for P53
 SEQ ID NO: 57 is the determined cDNA sequence for P55
 SEQ ID NO: 58 is the determined cDNA sequence for P60
 25 SEQ ID NO: 59 is the determined cDNA sequence for P64
 SEQ ID NO: 60 is the determined cDNA sequence for P65
 SEQ ID NO: 61 is the determined cDNA sequence for P73
 SEQ ID NO: 62 is the determined cDNA sequence for P75
 SEQ ID NO: 63 is the determined cDNA sequence for P76

SEQ ID NO: 64 is the determined cDNA sequence for P79

SEQ ID NO: 65 is the determined cDNA sequence for P84

SEQ ID NO: 66 is the determined cDNA sequence for P68

5 as P704P)

SEQ ID NO: 68 is the determined cDNA sequence for P82

SEQ ID NO: 69 is the determined cDNA sequence for U1-3064

SEQ ID NO: 70 is the determined cDNA sequence for U1-3065

SEQ ID NO: 71 is the determined cDNA sequence for V1-3692

10 SEQ ID NO: 72 is the determined cDNA sequence for 1A-3905

SEQ ID NO: 73 is the determined cDNA sequence for V1-3686

SEQ ID NO: 74 is the determined cDNA sequence for R1-2330

SEQ ID NO: 75 is the determined cDNA sequence for 1B-3976

SEQ ID NO: 76 is the determined cDNA sequence for V1-3679

15 SEQ ID NO: 77 is the determined cDNA sequence for 1G-4736

SEQ ID NO: 78 is the determined cDNA sequence for 1G-4738

SEQ ID NO: 79 is the determined cDNA sequence for 1G-4741

SEQ ID NO: 80 is the determined cDNA sequence for 1G-4744

SEQ ID NO: 81 is the determined cDNA sequence for 1G-4734

20 SEQ ID NO: 82 is the determined cDNA sequence for 1H-4774

SEQ ID NO: 83 is the determined cDNA sequence for 1H-4781

SEQ ID NO: 84 is the determined cDNA sequence for 1H-4785

SEQ ID NO: 85 is the determined cDNA sequence for 1H-4787

SEQ ID NO: 86 is the determined cDNA sequence for 1H-4796

25 SEQ ID NO: 87 is the determined cDNA sequence for 1I-4807

SEQ ID NO: 88 is the determined cDNA sequence for 1I-4810

SEQ ID NO: 89 is the determined cDNA sequence for 1I-4811

SEQ ID NO: 90 is the determined cDNA sequence for 1J-4876

SEQ ID NO: 91 is the determined cDNA sequence for 1K-4884

- SEQ ID NO: 92 is the determined cDNA sequence for 1K-4896
- SEQ ID NO: 93 is the determined cDNA sequence for 1G-4761
- SEQ ID NO: 94 is the determined cDNA sequence for 1G-4762
- SEQ ID NO: 95 is the determined cDNA sequence for 1H-4766
- 5 SEQ ID NO: 96 is the determined cDNA sequence for 1H-4770
- SEQ ID NO: 97 is the determined cDNA sequence for 1H-4771
- SEQ ID NO: 98 is the determined cDNA sequence for 1H-4772
- SEQ ID NO: 99 is the determined cDNA sequence for 1D-4297
- SEQ ID NO: 100 is the determined cDNA sequence for 1D-4309
- 10 SEQ ID NO: 101 is the determined cDNA sequence for 1D.1-4278
- SEQ ID NO: 102 is the determined cDNA sequence for 1D-4288
- SEQ ID NO: 103 is the determined cDNA sequence for 1D-4283
- SEQ ID NO: 104 is the determined cDNA sequence for 1D-4304
- SEQ ID NO: 105 is the determined cDNA sequence for 1D-4296
- 15 SEQ ID NO: 106 is the determined cDNA sequence for 1D-4280
- SEQ ID NO: 107 is the determined full length cDNA sequence for F1-12
(also referred to as P504S)
- SEQ ID NO: 108 is the predicted amino acid sequence for F1-12
- SEQ ID NO: 109 is the determined full length cDNA sequence for J1-17
- 20 SEQ ID NO: 110 is the determined full length cDNA sequence for L1-12
(also referred to as P501S)
- SEQ ID NO: 111 is the determined full length cDNA sequence for N1-1862
(also referred to as P503S)
- SEQ ID NO: 112 is the predicted amino acid sequence for J1-17
- 25 SEQ ID NO: 113 is the predicted amino acid sequence for L1-12 (also
referred to as P501S)
- SEQ ID NO: 114 is the predicted amino acid sequence for N1-1862 (also
referred to as P503S)
- SEQ ID NO: 115 is the determined cDNA sequence for P89

SEQ ID NO: 116 is the determined cDNA sequence for P90
 SEQ ID NO: 117 is the determined cDNA sequence for P92
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 SEQ ID NO: 119 is the determined cDNA sequence for P98
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 SEQ ID NO: 146 is the determined cDNA sequence for P219
 SEQ ID NO: 147 is the determined cDNA sequence for P237
 SEQ ID NO: 148 is the determined cDNA sequence for P239
 5 SEQ ID NO: 149 is the determined cDNA sequence for P248
 SEQ ID NO: 150 is the determined cDNA sequence for P251
 SEQ ID NO: 151 is the determined cDNA sequence for P255
 SEQ ID NO: 152 is the determined cDNA sequence for P256
 SEQ ID NO: 153 is the determined cDNA sequence for P259
 10 SEQ ID NO: 154 is the determined cDNA sequence for P260
 SEQ ID NO: 155 is the determined cDNA sequence for P263
 SEQ ID NO: 156 is the determined cDNA sequence for P264
 SEQ ID NO: 157 is the determined cDNA sequence for P266
 SEQ ID NO: 158 is the determined cDNA sequence for P270
 15 SEQ ID NO: 159 is the determined cDNA sequence for P272
 SEQ ID NO: 160 is the determined cDNA sequence for P278
 SEQ ID NO: 161 is the determined cDNA sequence for P105
 SEQ ID NO: 162 is the determined cDNA sequence for P107
 SEQ ID NO: 163 is the determined cDNA sequence for P137
 20 SEQ ID NO: 164 is the determined cDNA sequence for P194
 SEQ ID NO: 165 is the determined cDNA sequence for P195
 SEQ ID NO: 166 is the determined cDNA sequence for P196
 SEQ ID NO: 167 is the determined cDNA sequence for P220
 SEQ ID NO: 168 is the determined cDNA sequence for P234
 25 SEQ ID NO: 169 is the determined cDNA sequence for P235
 SEQ ID NO: 170 is the determined cDNA sequence for P243
 SEQ ID NO: 171 is the determined cDNA sequence for P703P-DE1
 SEQ ID NO: 172 is the predicted amino acid sequence for P703P-DE1
 SEQ ID NO: 173 is the determined cDNA sequence for P703P-DE2

SEQ ID NO: 174 is the determined cDNA sequence for P703P-DE6
 SEQ ID NO: 175 is the determined cDNA sequence for P703P-DE13
 SEQ ID NO: 176 is the predicted amino acid sequence for P703P-DE13
 SEQ ID NO: 177 is the determined cDNA sequence for P703P-DE14
 5 SEQ ID NO: 178 is the predicted amino acid sequence for P703P-DE14
 SEQ ID NO: 179 is the determined extended cDNA sequence for 1G-4736
 SEQ ID NO: 180 is the determined extended cDNA sequence for 1G-4738
 SEQ ID NO: 181 is the determined extended cDNA sequence for 1G-4741
 SEQ ID NO: 182 is the determined extended cDNA sequence for 1G-4744
 10 SEQ ID NO: 183 is the determined extended cDNA sequence for 1H-4774
 SEQ ID NO: 184 is the determined extended cDNA sequence for 1H-4781
 SEQ ID NO: 185 is the determined extended cDNA sequence for 1H-4785
 SEQ ID NO: 186 is the determined extended cDNA sequence for 1H-4787
 SEQ ID NO: 187 is the determined extended cDNA sequence for 1H-4796
 15 SEQ ID NO: 188 is the determined extended cDNA sequence for 1I-4807
 SEQ ID NO: 189 is the determined 3' cDNA sequence for 1I-4810
 SEQ ID NO: 190 is the determined 3' cDNA sequence for 1I-4811
 SEQ ID NO: 191 is the determined extended cDNA sequence for 1J-4876
 SEQ ID NO: 192 is the determined extended cDNA sequence for 1K-4884
 20 SEQ ID NO: 193 is the determined extended cDNA sequence for 1K-4896
 SEQ ID NO: 194 is the determined extended cDNA sequence for 1G-4761
 SEQ ID NO: 195 is the determined extended cDNA sequence for 1G-4762
 SEQ ID NO: 196 is the determined extended cDNA sequence for 1H-4766
 SEQ ID NO: 197 is the determined 3' cDNA sequence for 1H-4770
 25 SEQ ID NO: 198 is the determined 3' cDNA sequence for 1H-4771
 SEQ ID NO: 199 is the determined extended cDNA sequence for 1H-4772
 SEQ ID NO: 200 is the determined extended cDNA sequence for 1D-4309
 SEQ ID NO: 201 is the determined extended cDNA sequence for 1D.1-4278
 SEQ ID NO: 202 is the determined extended cDNA sequence for 1D-4288

SEQ ID NO: 203 is the determined extended cDNA sequence for 1D-4283
 SEQ ID NO: 204 is the determined extended cDNA sequence for 1D-4304
 SEQ ID NO: 205 is the determined extended cDNA sequence for 1D-4296
 SEQ ID NO: 206 is the determined extended cDNA sequence for 1D-4280
 5 SEQ ID NO: 207 is the determined cDNA sequence for 10-d8fwd
 SEQ ID NO: 208 is the determined cDNA sequence for 10-H10con
 SEQ ID NO: 209 is the determined cDNA sequence for 11-C8rev
 SEQ ID NO: 210 is the determined cDNA sequence for 7.g6fwd
 SEQ ID NO: 211 is the determined cDNA sequence for 7.g6rev
 10 SEQ ID NO: 212 is the determined cDNA sequence for 8-b5fwd
 SEQ ID NO: 213 is the determined cDNA sequence for 8-b5rev
 SEQ ID NO: 214 is the determined cDNA sequence for 8-b6fwd
 SEQ ID NO: 215 is the determined cDNA sequence for 8-b6 rev
 SEQ ID NO: 216 is the determined cDNA sequence for 8-d4fwd
 15 SEQ ID NO: 217 is the determined cDNA sequence for 8-d9rev
 SEQ ID NO: 218 is the determined cDNA sequence for 8-g3fwd
 SEQ ID NO: 219 is the determined cDNA sequence for 8-g3rev
 SEQ ID NO: 220 is the determined cDNA sequence for 8-h11rev
 SEQ ID NO: 221 is the determined cDNA sequence for g-f12fwd
 20 SEQ ID NO: 222 is the determined cDNA sequence for g-f3rev
 SEQ ID NO: 223 is the determined cDNA sequence for P509S
 SEQ ID NO: 224 is the determined cDNA sequence for P510S
 SEQ ID NO: 225 is the determined cDNA sequence for P703DE5
 SEQ ID NO: 226 is the determined cDNA sequence for 9-A11
 25 SEQ ID NO: 227 is the determined cDNA sequence for 8-C6
 SEQ ID NO: 228 is the determined cDNA sequence for 8-H7
 SEQ ID NO: 229 is the determined cDNA sequence for JPTPN13
 SEQ ID NO: 230 is the determined cDNA sequence for JPTPN14
 SEQ ID NO: 231 is the determined cDNA sequence for JPTPN23

SEQ ID NO: 232 is the determined cDNA sequence for JPTPN24
 SEQ ID NO: 233 is the determined cDNA sequence for JPTPN25
 SEQ ID NO: 234 is the determined cDNA sequence for JPTPN30
 SEQ ID NO: 235 is the determined cDNA sequence for JPTPN34
 5 SEQ ID NO: 236 is the determined cDNA sequence for PTPN35
 SEQ ID NO: 237 is the determined cDNA sequence for JPTPN36
 SEQ ID NO: 238 is the determined cDNA sequence for JPTPN38
 SEQ ID NO: 239 is the determined cDNA sequence for JPTPN39
 SEQ ID NO: 240 is the determined cDNA sequence for JPTPN40
 10 SEQ ID NO: 241 is the determined cDNA sequence for JPTPN41
 SEQ ID NO: 242 is the determined cDNA sequence for JPTPN42
 SEQ ID NO: 243 is the determined cDNA sequence for JPTPN45
 SEQ ID NO: 244 is the determined cDNA sequence for JPTPN46
 SEQ ID NO: 245 is the determined cDNA sequence for JPTPN51
 15 SEQ ID NO: 246 is the determined cDNA sequence for JPTPN56
 SEQ ID NO: 247 is the determined cDNA sequence for PTPN64
 SEQ ID NO: 248 is the determined cDNA sequence for JPTPN65
 SEQ ID NO: 249 is the determined cDNA sequence for JPTPN67
 SEQ ID NO: 250 is the determined cDNA sequence for JPTPN76
 20 SEQ ID NO: 251 is the determined cDNA sequence for JPTPN84
 SEQ ID NO: 252 is the determined cDNA sequence for JPTPN85
 SEQ ID NO: 253 is the determined cDNA sequence for JPTPN86
 SEQ ID NO: 254 is the determined cDNA sequence for JPTPN87
 SEQ ID NO: 255 is the determined cDNA sequence for JPTPN88
 25 SEQ ID NO: 256 is the determined cDNA sequence for JP1F1
 SEQ ID NO: 257 is the determined cDNA sequence for JP1F2
 SEQ ID NO: 258 is the determined cDNA sequence for JP1C2
 SEQ ID NO: 259 is the determined cDNA sequence for JP1B1
 SEQ ID NO: 260 is the determined cDNA sequence for JP1B2

SEQ ID NO: 261 is the determined cDNA sequence for JP1D3
 SEQ ID NO: 262 is the determined cDNA sequence for JP1A4
 SEQ ID NO: 263 is the determined cDNA sequence for JP1F5
 SEQ ID NO: 264 is the determined cDNA sequence for JP1E6
 5 SEQ ID NO: 265 is the determined cDNA sequence for JP1D6
 SEQ ID NO: 266 is the determined cDNA sequence for JP1B5
 SEQ ID NO: 267 is the determined cDNA sequence for JP1A6
 SEQ ID NO: 268 is the determined cDNA sequence for JP1E8
 SEQ ID NO: 269 is the determined cDNA sequence for JP1D7
 10 SEQ ID NO: 270 is the determined cDNA sequence for JP1D9
 SEQ ID NO: 271 is the determined cDNA sequence for JP1C10
 SEQ ID NO: 272 is the determined cDNA sequence for JP1A9
 SEQ ID NO: 273 is the determined cDNA sequence for JP1F12
 SEQ ID NO: 274 is the determined cDNA sequence for JP1E12
 15 SEQ ID NO: 275 is the determined cDNA sequence for JP1D11
 SEQ ID NO: 276 is the determined cDNA sequence for JP1C11
 SEQ ID NO: 277 is the determined cDNA sequence for JP1C12
 SEQ ID NO: 278 is the determined cDNA sequence for JP1B12
 SEQ ID NO: 279 is the determined cDNA sequence for JP1A12
 20 SEQ ID NO: 280 is the determined cDNA sequence for JP8G2
 SEQ ID NO: 281 is the determined cDNA sequence for JP8H1
 SEQ ID NO: 282 is the determined cDNA sequence for JP8H2
 SEQ ID NO: 283 is the determined cDNA sequence for JP8A3
 SEQ ID NO: 284 is the determined cDNA sequence for JP8A4
 25 SEQ ID NO: 285 is the determined cDNA sequence for JP8C3
 SEQ ID NO: 286 is the determined cDNA sequence for JP8G4
 SEQ ID NO: 287 is the determined cDNA sequence for JP8B6
 SEQ ID NO: 288 is the determined cDNA sequence for JP8D6
 SEQ ID NO: 289 is the determined cDNA sequence for JP8F5

SEQ ID NO: 290 is the determined cDNA sequence for JP8A8
 SEQ ID NO: 291 is the determined cDNA sequence for JP8C7
 SEQ ID NO: 292 is the determined cDNA sequence for JP8D7
 SEQ ID NO: 293 is the determined cDNA sequence for P8D8
 5 SEQ ID NO: 294 is the determined cDNA sequence for JP8E7
 SEQ ID NO: 295 is the determined cDNA sequence for JP8F8
 SEQ ID NO: 296 is the determined cDNA sequence for JP8G8
 SEQ ID NO: 297 is the determined cDNA sequence for JP8B10
 SEQ ID NO: 298 is the determined cDNA sequence for JP8C10
 10 SEQ ID NO: 299 is the determined cDNA sequence for JP8E9
 SEQ ID NO: 300 is the determined cDNA sequence for JP8E10
 SEQ ID NO: 301 is the determined cDNA sequence for JP8F9
 SEQ ID NO: 302 is the determined cDNA sequence for JP8H9
 SEQ ID NO: 303 is the determined cDNA sequence for JP8C12
 15 SEQ ID NO: 304 is the determined cDNA sequence for JP8E11
 SEQ ID NO: 305 is the determined cDNA sequence for JP8E12
 SEQ ID NO: 306 is the amino acid sequence for the peptide PS2#12
 SEQ ID NO: 307 is the determined cDNA sequence for P711P
 SEQ ID NO: 308 is the determined cDNA sequence for P712P
 20 SEQ ID NO: 309 is the determined cDNA sequence for CLONE23
 SEQ ID NO: 310 is the determined cDNA sequence for P774P
 SEQ ID NO: 311 is the determined cDNA sequence for P775P
 SEQ ID NO: 312 is the determined cDNA sequence for P715P
 SEQ ID NO: 313 is the determined cDNA sequence for P710P
 25 SEQ ID NO: 314 is the determined cDNA sequence for P767P
 SEQ ID NO: 315 is the determined cDNA sequence for P768P
 SEQ ID NO: 316-325 are the determined cDNA sequences of previously
 isolated genes
 SEQ ID NO: 326 is the determined cDNA sequence for P703PDE5

- SEQ ID NO: 327 is the predicted amino acid sequence for P703PDE5
- SEQ ID NO: 328 is the determined cDNA sequence for P703P6.26
- SEQ ID NO: 329 is the predicted amino acid sequence for P703P6.26
- SEQ ID NO: 330 is the determined cDNA sequence for P703PX-23
- 5 SEQ ID NO: 331 is the predicted amino acid sequence for P703PX-23
- SEQ ID NO: 332 is the determined full length cDNA sequence for P509S
- SEQ ID NO: 333 is the determined extended cDNA sequence for P707P
(also referred to as 11-C9)
- SEQ ID NO: 334 is the determined cDNA sequence for P714P
- 10 SEQ ID NO: 335 is the determined cDNA sequence for P705P (also
referred to as 9-F3)
- SEQ ID NO: 336 is the predicted amino acid sequence for P705P
- SEQ ID NO: 337 is the amino acid sequence of the peptide P1S#10
- SEQ ID NO: 338 is the amino acid sequence of the peptide p5
- 15 SEQ ID NO: 339 is the predicted amino acid sequence of P509S
- SEQ ID NO: 340 is the determined cDNA sequence for P778P
- SEQ ID NO: 341 is the determined cDNA sequence for P786P
- SEQ ID NO: 342 is the determined cDNA sequence for P789P
- SEQ ID NO: 343 is the determined cDNA sequence for a clone showing
20 homology to Homo sapiens MM46 mRNA
- SEQ ID NO: 344 is the determined cDNA sequence for a clone showing
homology to Homo sapiens TNF-alpha stimulated ABC protein (ABC50) mRNA
- SEQ ID NO: 345 is the determined cDNA sequence for a clone showing
homology to Homo sapiens mRNA for E-cadherin
- 25 SEQ ID NO: 346 is the determined cDNA sequence for a clone showing
homology to Human nuclear-encoded mitochondrial serine hydroxymethyltransferase
(SHMT)
- SEQ ID NO: 347 is the determined cDNA sequence for a clone showing
homology to Homo sapiens natural resistance-associated macrophage protein2 (NRAMP2)

SEQ ID NO: 348 is the determined cDNA sequence for a clone showing homology to Homo sapiens phosphoglucomutase-related protein (PGMRP)

SEQ ID NO: 349 is the determined cDNA sequence for a clone showing homology to Human mRNA for proteosome subunit p40

5 SEQ ID NO: 350 is the determined cDNA sequence for P777P
 SEQ ID NO: 351 is the determined cDNA sequence for P779P
 SEQ ID NO: 352 is the determined cDNA sequence for P790P
 SEQ ID NO: 353 is the determined cDNA sequence for P784P
 SEQ ID NO: 354 is the determined cDNA sequence for P776P
 10 SEQ ID NO: 355 is the determined cDNA sequence for P780P
 SEQ ID NO: 356 is the determined cDNA sequence for P544S
 SEQ ID NO: 357 is the determined cDNA sequence for P745S
 SEQ ID NO: 358 is the determined cDNA sequence for P782P
 SEQ ID NO: 359 is the determined cDNA sequence for P783P
 15 SEQ ID NO: 360 is the determined cDNA sequence for unknown 17984
 SEQ ID NO: 361 is the determined cDNA sequence for P787P
 SEQ ID NO: 362 is the determined cDNA sequence for P788P
 SEQ ID NO: 363 is the determined cDNA sequence for unknown 17994
 SEQ ID NO: 364 is the determined cDNA sequence for P781P
 20 SEQ ID NO: 365 is the determined cDNA sequence for P785P
 SEQ ID NO: 366-375 are the determined cDNA sequences for splice variants of B305D.

SEQ ID NO: 376 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 366.

25 SEQ ID NO: 377 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 372.

SEQ ID NO: 378 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 373.

SEQ ID NO: 379 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 374.

SEQ ID NO: 380 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 375.

- 5 SEQ ID NO: 381 is the determined cDNA sequence for B716P.
 SEQ ID NO: 382 is the determined full-length cDNA sequence for P711P.
 SEQ ID NO: 383 is the predicted amino acid sequence for P711P.
 SEQ ID NO: 384 is the cDNA sequence for P1000C.
 SEQ ID NO: 385 is the cDNA sequence for CGI-82.
- 10 SEQ ID NO:386 is the cDNA sequence for 23320.
 SEQ ID NO:387 is the cDNA sequence for CGI-69.
 SEQ ID NO:388 is the cDNA sequence for L-iditol-2-dehydrogenase.
 SEQ ID NO:389 is the cDNA sequence for 23379.
 SEQ ID NO:390 is the cDNA sequence for 23381.
- 15 SEQ ID NO:391 is the cDNA sequence for KIAA0122.
 SEQ ID NO:392 is the cDNA sequence for 23399.
 SEQ ID NO:393 is the cDNA sequence for a previously identified gene.
 SEQ ID NO:394 is the cDNA sequence for HCLBP.
 SEQ ID NO:395 is the cDNA sequence for transglutaminase.
- 20 SEQ ID NO:396 is the cDNA sequence for a previously identified gene.
 SEQ ID NO:397 is the cDNA sequence for PAP.
 SEQ ID NO:398 is the cDNA sequence for Ets transcription factor PDEF.
 SEQ ID NO:399 is the cDNA sequence for hTGR.
 SEQ ID NO:400 is the cDNA sequence for KIAA0295.
- 25 SEQ ID NO:401 is the cDNA sequence for 22545.
 SEQ ID NO:402 is the cDNA sequence for 22547.
 SEQ ID NO:403 is the cDNA sequence for 22548.
 SEQ ID NO:404 is the cDNA sequence for 22550.
 SEQ ID NO:405 is the cDNA sequence for 22551.

SEQ ID NO:406 is the cDNA sequence for 22552.

SEQ ID NO:407 is the cDNA sequence for 22553 (also known as P1020C).

SEQ ID NO:408 is the cDNA sequence for 22558.

SEQ ID NO:409 is the cDNA sequence for 22562.

5 SEQ ID NO:410 is the cDNA sequence for 22565.

SEQ ID NO:411 is the cDNA sequence for 22567.

SEQ ID NO:412 is the cDNA sequence for 22568.

SEQ ID NO:413 is the cDNA sequence for 22570.

SEQ ID NO:414 is the cDNA sequence for 22571.

10 SEQ ID NO:415 is the cDNA sequence for 22572.

SEQ ID NO:416 is the cDNA sequence for 22573.

SEQ ID NO:417 is the cDNA sequence for 22573.

SEQ ID NO:418 is the cDNA sequence for 22575.

SEQ ID NO:419 is the cDNA sequence for 22580.

15 SEQ ID NO:420 is the cDNA sequence for 22581.

SEQ ID NO:421 is the cDNA sequence for 22582.

SEQ ID NO:422 is the cDNA sequence for 22583.

SEQ ID NO:423 is the cDNA sequence for 22584.

SEQ ID NO:424 is the cDNA sequence for 22585.

20 SEQ ID NO:425 is the cDNA sequence for 22586.

SEQ ID NO:426 is the cDNA sequence for 22587.

SEQ ID NO:427 is the cDNA sequence for 22588.

SEQ ID NO:428 is the cDNA sequence for 22589.

SEQ ID NO:429 is the cDNA sequence for 22590.

25 SEQ ID NO:430 is the cDNA sequence for 22591.

SEQ ID NO:431 is the cDNA sequence for 22592.

SEQ ID NO:432 is the cDNA sequence for 22593.

SEQ ID NO:433 is the cDNA sequence for 22594.

SEQ ID NO:434 is the cDNA sequence for 22595.

SEQ ID NO:435 is the cDNA sequence for 22596.
 SEQ ID NO:436 is the cDNA sequence for 22847.
 SEQ ID NO:437 is the cDNA sequence for 22848.
 SEQ ID NO:438 is the cDNA sequence for 22849.
 5 SEQ ID NO:439 is the cDNA sequence for 22851.
 SEQ ID NO:440 is the cDNA sequence for 22852.
 SEQ ID NO:441 is the cDNA sequence for 22853.
 SEQ ID NO:442 is the cDNA sequence for 22854.
 SEQ ID NO:443 is the cDNA sequence for 22855.
 10 SEQ ID NO:444 is the cDNA sequence for 22856.
 SEQ ID NO:445 is the cDNA sequence for 22857.
 SEQ ID NO:446 is the cDNA sequence for 23601.
 SEQ ID NO:447 is the cDNA sequence for 23602.
 SEQ ID NO:448 is the cDNA sequence for 23605.
 15 SEQ ID NO:449 is the cDNA sequence for 23606.
 SEQ ID NO:450 is the cDNA sequence for 23612.
 SEQ ID NO:451 is the cDNA sequence for 23614.
 SEQ ID NO:452 is the cDNA sequence for 23618.
 SEQ ID NO:453 is the cDNA sequence for 23622.
 20 SEQ ID NO:454 is the cDNA sequence for folate hydrolase.
 SEQ ID NO:455 is the cDNA sequence for LIM protein.
 SEQ ID NO:456 is the cDNA sequence for a known gene.
 SEQ ID NO:457 is the cDNA sequence for a known gene.
 SEQ ID NO:458 is the cDNA sequence for a previously identified gene.
 25 SEQ ID NO:459 is the cDNA sequence for 23045.
 SEQ ID NO:460 is the cDNA sequence for 23032.
 SEQ ID NO:461 is the cDNA sequence for 23054.
 SEQ ID NO:462-467 are cDNA sequences for known genes.
 SEQ ID NO:468-471 are cDNA sequences for P710P.

SEQ ID NO:472 is a cDNA sequence for P1001C.

SEQ ID NO: 473 is the determined cDNA sequence for a first splice variant of P775P (referred to as 27505).

5 SEQ ID NO: 474 is the determined cDNA sequence for a second splice variant of P775P (referred to as 19947).

SEQ ID NO: 475 is the determined cDNA sequence for a third splice variant of P775P (referred to as 19941).

SEQ ID NO: 476 is the determined cDNA sequence for a fourth splice variant of P775P (referred to as 19937).

10 SEQ ID NO: 477 is a first predicted amino acid sequence encoded by the sequence of SEQ ID NO: 474.

SEQ ID NO: 478 is a second predicted amino acid sequence encoded by the sequence of SEQ ID NO: 474.

15 SEQ ID NO: 479 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 475.

SEQ ID NO: 480 is a first predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

SEQ ID NO: 481 is a second predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

20 SEQ ID NO: 482 is a third predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

SEQ ID NO: 483 is a fourth predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

25 SEQ ID NO: 484 is the first 30 amino acids of the *M. tuberculosis* antigen Ra12.

SEQ ID NO: 485 is the PCR primer AW025.

SEQ ID NO: 486 is the PCR primer AW003.

SEQ ID NO: 487 is the PCR primer AW027.

SEQ ID NO: 488 is the PCR primer AW026.

SEQ ID NO: 489-501 are peptides employed in epitope mapping studies.

SEQ ID NO: 502 is the determined cDNA sequence of the complementarity determining region for the anti-P503S monoclonal antibody 20D4.

5 SEQ ID NO: 503 is the determined cDNA sequence of the complementarity determining region for the anti-P503S monoclonal antibody JA1.

SEQ ID NO: 504 & 505 are peptides employed in epitope mapping studies.

SEQ ID NO: 506 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 8H2.

10 SEQ ID NO: 507 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 7H8.

SEQ ID NO: 508 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 2D4.

SEQ ID NO: 509-522 are peptides employed in epitope mapping studies.

15 SEQ ID NO: 523 is a mature form of P703P used to raise antibodies against P703P.

SEQ ID NO: 524 is the putative full-length cDNA sequence of P703P.

SEQ ID NO: 525 is the predicted amino acid sequence encoded by SEQ ID NO: 524.

SEQ ID NO: 526 is the full-length cDNA sequence for P790P.

20 SEQ ID NO: 527 is the predicted amino acid sequence for P790P.

SEQ ID NO: 528 & 529 are PCR primers.

SEQ ID NO: 530 is the cDNA sequence of a splice variant of SEQ ID NO: 366.

25 SEQ ID NO: 531 is the cDNA sequence of the open reading frame of SEQ ID NO: 530.

SEQ ID NO: 532 is the predicted amino acid encoded by the sequence of SEQ ID NO: 531.

SEQ ID NO: 533 is the DNA sequence of a putative ORF of P775P.

SEQ ID NO: 534 is the predicted amino acid sequence encoded by SEQ ID NO: 533.

SEQ ID NO: 535 is a first full-length cDNA sequence for P510S.

SEQ ID NO: 536 is a second full-length cDNA sequence for P510S.

5 SEQ ID NO: 537 is the predicted amino acid sequence encoded by SEQ ID NO: 535.

SEQ ID NO: 538 is the predicted amino acid sequence encoded by SEQ ID NO: 536.

SEQ ID NO: 539 is the peptide P501S-370.

10 SEQ ID NO: 540 is the peptide P501S-376.

SEQ ID NO: 541-551 are epitopes of P501S.

SEQ ID NO: 552 is an extended cDNA sequence for P712P.

SEQ ID NO: 553-568 are the amino acid sequences encoded by predicted open reading frames within SEQ ID NO: 552.

15 SEQ ID NO: 569 is an extended cDNA sequence for P776P.

SEQ ID NO: 570 is the determined cDNA sequence for a splice variant of P776P referred to as contig 6.

SEQ ID NO: 571 is the determined cDNA sequence for a splice variant of P776P referred to as contig 7.

20 SEQ ID NO: 572 is the determined cDNA sequence for a splice variant of P776P referred to as contig 14.

SEQ ID NO: 573 is the amino acid sequence encoded by a first predicted ORF of SEQ ID NO: 570.

25 SEQ ID NO: 574 is the amino acid sequence encoded by a second predicted ORF of SEQ ID NO: 570.

SEQ ID NO: 575 is the amino acid sequence encoded by a predicted ORF of SEQ ID NO: 571.

SEQ ID NO: 576-586 are amino acid sequences encoded by predicted ORFs of SEQ ID NO: 569.

SEQ ID NO: 587 is a DNA consensus sequence of the sequences of P767P and P777P.

SEQ ID NO: 588-590 are amino acid sequences encoded by predicted ORFs of SEQ ID NO: 587.

5 SEQ ID NO: 591 is an extended cDNA sequence for P1020C.

SEQ ID NO: 592 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: P1020C.

SEQ ID NO: 593 is a splice variant of P775P referred to as 50748.

10 SEQ ID NO: 594 is a splice variant of P775P referred to as 50717. SEQ ID NO: 595 is a splice variant of P775P referred to as 45985.

SEQ ID NO: 596 is a splice variant of P775P referred to as 38769.

SEQ ID NO: 597 is a splice variant of P775P referred to as 37922.

SEQ ID NO: 598 is a splice variant of P510S referred to as 49274.

SEQ ID NO: 599 is a splice variant of P510S referred to as 39487.

15 SEQ ID NO: 600 is a splice variant of P504S referred to as 5167.16.

SEQ ID NO: 601 is a splice variant of P504S referred to as 5167.1.

SEQ ID NO: 602 is a splice variant of P504S referred to as 5163.46.

SEQ ID NO: 603 is a splice variant of P504S referred to as 5163.42.

SEQ ID NO: 604 is a splice variant of P504S referred to as 5163.34.

20 SEQ ID NO: 605 is a splice variant of P504S referred to as 5163.17.

SEQ ID NO: 606 is a splice variant of P501S referred to as 10640.

SEQ ID NO: 607-615 are the sequences of PCR primers.

SEQ ID NO: 616 is the determined cDNA sequence of a fusion of P703P and PSA.

25 SEQ ID NO: 617 is the amino acid sequence of the fusion of P703P and PSA.

SEQ ID NO: 618-689 are determined cDNA sequences of prostate-specific clones.

SEQ ID NO: 690 is the cDNA sequence of the gene DD3.

SEQ ID NO: 691-697 are determined cDNA sequences of prostate-specific clones.

SEQ ID NO: 698 is an extended cDNA sequence for P714P.

SEQ ID NO: 699-701 are the cDNA sequences for splice variants of P704P.

5 SEQ ID NO: 702 is the cDNA sequence of a spliced variant of P553S referred to as P553S-14.

SEQ ID NO: 703 is the cDNA sequence of a spliced variant of P553S referred to as P553S-12.

10 SEQ ID NO: 704 is the cDNA sequence of a spliced variant of P553S referred to as P553S-10.

SEQ ID NO: 705 is the cDNA sequence of a spliced variant of P553S referred to as P553S-6.

SEQ ID NO: 706 is the amino acid sequence encoded by SEQ ID NO: 705.

SEQ ID NO: 707 is the amino acid sequence encoded by SEQ ID NO: 702

15 SEQ ID NO: 708 is a second amino acid sequence encoded by SEQ ID NO: 702.

SEQ ID NO: 709-772 are determined cDNA sequences of prostate-specific clones.

SEQ ID NO: 773 is a first full-length cDNA sequence for prostate-specific transglutaminase gene (also referred to herein as P558S).

20 SEQ ID NO: 774 is a second full-length cDNA sequence for prostate-specific transglutaminase gene.

SEQ ID NO: 775 is the amino acid sequence encoded by the sequence of SEQ ID NO: 773.

25 SEQ ID NO: 776 is the amino acid sequence encoded by the sequence of SEQ ID NO: 774.

SEQ ID NO: 777 is the full-length cDNA sequence for P788P.

SEQ ID NO: 778 is the amino acid sequence encoded by SEQ ID NO: 777.

SEQ ID NO: 779 is the determined cDNA sequence for a polymorphic variant of P788P.

- SEQ ID NO: 780 is the amino acid sequence encoded by SEQ ID NO: 779.
 SEQ ID NO: 781 is the amino acid sequence of peptide 4 from P703P.
 SEQ ID NO: 782 is the cDNA sequence that encodes peptide 4 from P703P.
 SEQ ID NO: 783-798 are the cDNA sequence encoding epitopes of P703P.
 5 SEQ ID NO: 799-814 are the amino acid sequences of epitopes of P703P.
 SEQ ID NO: 815 and 816 are PCR primers.
 SEQ ID NO: 817 is the cDNA sequence encoding an N-terminal portion of
 P788P expressed in *E. coli*.
 SEQ ID NO: 818 is the amino acid sequence of the N-terminal portion of
 10 P788P expressed in *E. coli*.
 SEQ ID NO: 819 is the amino acid sequence of the *M. tuberculosis* antigen
 Ra12.
 SEQ ID NO: 820 and 821 are PCR primers.
 SEQ ID NO: 822 is the cDNA sequence for the Ra12-P510S-C construct.
 15 SEQ ID NO: 823 is the cDNA sequence for the P510S-C construct.
 SEQ ID NO: 824 is the cDNA sequence for the P510S-E3 construct.
 SEQ ID NO: 825 is the amino acid sequence for the Ra12-P510S-C
 construct.
 SEQ ID NO: 826 is the amino acid sequence for the P510S-C construct.
 20 SEQ ID NO: 827 is the amino acid sequence for the P510S-E3 construct.
 SEQ ID NO: 828-833 are PCR primers.
 SEQ ID NO: 834 is the cDNA sequence of the construct Ra12-P775P-
 ORF3.
 SEQ ID NO: 835 is the amino acid sequence of the construct Ra12-P775P-
 25 ORF3.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for using the compositions, for example in the therapy and diagnosis of

cancer, such as prostate cancer. Certain illustrative compositions described herein include prostate-specific polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies, antigen presenting cells (APCs) and/or immune system cells (*e.g.*, T cells). A "prostate-specific protein," as the term is used herein, refers generally to a protein that is expressed in prostate cells at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in other normal tissues, as determined using a representative assay provided herein. Certain prostate-specific proteins are tumor proteins that react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera of a patient afflicted with prostate cancer.

Therefore, in accordance with the above, and as described further below, the present invention provides illustrative polynucleotide compositions having sequences set forth in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777, 789, 817, 823 and 824, illustrative polypeptide compositions having amino acid sequences set forth in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 706-708, 775, 776, 778, 780, 781, 811, 814, 818, 826 and 827, antibody compositions capable of binding such polypeptides, and numerous additional embodiments employing such compositions, for example in the detection, diagnosis and/or therapy of human prostate cancer.

POLYNUCLEOTIDE COMPOSITIONS

As used herein, the terms "DNA segment" and "polynucleotide" refer to a DNA molecule that has been isolated free of total genomic DNA of a particular species. Therefore, a DNA segment encoding a polypeptide refers to a DNA segment that contains one or more coding sequences yet is substantially isolated away from, or purified free from, total genomic DNA of the species from which the DNA segment is obtained. Included within the terms "DNA segment" and "polynucleotide" are DNA segments and smaller

fragments of such segments, and also recombinant vectors, including, for example, plasmids, cosmids, phagemids, phage, viruses, and the like.

As will be understood by those skilled in the art, the DNA segments of this invention can include genomic sequences, extra-genomic and plasmid-encoded sequences
 5 and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may be naturally isolated, or modified synthetically by the hand of man.

"Isolated," as used herein, means that a polynucleotide is substantially away from other coding sequences, and that the DNA segment does not contain large portions of
 10 unrelated coding DNA, such as large chromosomal fragments or other functional genes or polypeptide coding regions. Of course, this refers to the DNA segment as originally isolated, and does not exclude genes or coding regions later added to the segment by the hand of man.

As will be recognized by the skilled artisan, polynucleotides may be single-
 15 stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may,
 20 but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a prostate-specific protein or a portion thereof) or may comprise a variant, or a biological or antigenic functional equivalent of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or
 25 insertions, as further described below, preferably such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native tumor protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. The term "variants" also encompasses homologous genes of xenogenic origin.

When comparing polynucleotide or polypeptide sequences, two sequences are said to be “identical” if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A “comparison window” as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) *Atlas of Protein Sequence and Structure*, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenies pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* 4:11-17; Robinson, E.D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA* 80:726-730.

Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP,

BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al.* (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul *et al.* (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides and polypeptides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. In one illustrative example, cumulative scores can be calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always <0). For amino acid sequences, a scoring matrix can be used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments, (B) of 50, expectation (E) of 10, M=5, N=-4 and a comparison of both strands.

Preferably, the “percentage of sequence identity” is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical

nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

5 Therefore, the present invention encompasses polynucleotide and polypeptide sequences having substantial identity to the sequences disclosed herein, for example those comprising at least 50% sequence identity, preferably at least 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher, sequence identity compared to a polynucleotide or polypeptide sequence of this invention using the
10 methods described herein, (*e.g.*, BLAST analysis using standard parameters, as described below). One skilled in this art will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and the like.

15 In additional embodiments, the present invention provides isolated polynucleotides and polypeptides comprising various lengths of contiguous stretches of sequence identical to or complementary to one or more of the sequences disclosed herein. For example, polynucleotides are provided by this invention that comprise at least about 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 400, 500 or 1000 or more contiguous nucleotides
20 of one or more of the sequences disclosed herein as well as all intermediate lengths there between. It will be readily understood that "intermediate lengths", in this context, means any length between the quoted values, such as 16, 17, 18, 19, *etc.*; 21, 22, 23, *etc.*; 30, 31, 32, *etc.*; 50, 51, 52, 53, *etc.*; 100, 101, 102, 103, *etc.*; 150, 151, 152, 153, *etc.*; including all integers through 200-500; 500-1,000, and the like.

25 The polynucleotides of the present invention, or fragments thereof, regardless of the length of the coding sequence itself, may be combined with other DNA sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length may vary considerably. It is therefore contemplated that a nucleic acid fragment of almost

any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant DNA protocol. For example, illustrative DNA segments with total lengths of about 10,000, about 5000, about 3000, about 2,000, about 1,000, about 500, about 200, about 100, about 50 base pairs in length, and the like,
 5 (including all intermediate lengths) are contemplated to be useful in many implementations of this invention.

In other embodiments, the present invention is directed to polynucleotides that are capable of hybridizing under moderately stringent conditions to a polynucleotide sequence provided herein, or a fragment thereof, or a complementary sequence thereof.
 10 Hybridization techniques are well known in the art of molecular biology. For purposes of illustration, suitable moderately stringent conditions for testing the hybridization of a polynucleotide of this invention with other polynucleotides include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X
 15 and 0.2X SSC containing 0.1% SDS.

Moreover, it will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that
 20 vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an
 25 altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

PROBES AND PRIMERS

In other embodiments of the present invention, the polynucleotide sequences provided herein can be advantageously used as probes or primers for nucleic acid hybridization. As such, it is contemplated that nucleic acid segments that comprise a
5 sequence region of at least about 15 nucleotide long contiguous sequence that has the same sequence as, or is complementary to, a 15 nucleotide long contiguous sequence disclosed herein will find particular utility. Longer contiguous identical or complementary sequences, *e.g.*, those of about 20, 30, 40, 50, 100, 200, 500, 1000 (including all intermediate lengths) and even up to full length sequences will also be of use in certain
10 embodiments.

The ability of such nucleic acid probes to specifically hybridize to a sequence of interest will enable them to be of use in detecting the presence of complementary sequences in a given sample. However, other uses are also envisioned, such as the use of the sequence information for the preparation of mutant species primers,
15 or primers for use in preparing other genetic constructions.

Polynucleotide molecules having sequence regions consisting of contiguous nucleotide stretches of 10-14, 15-20, 30, 50, or even of 100-200 nucleotides or so (including intermediate lengths as well), identical or complementary to a polynucleotide sequence disclosed herein, are particularly contemplated as hybridization probes for use in,
20 *e.g.*, Southern and Northern blotting. This would allow a gene product, or fragment thereof, to be analyzed, both in diverse cell types and also in various bacterial cells. The total size of fragment, as well as the size of the complementary stretch(es), will ultimately depend on the intended use or application of the particular nucleic acid segment. Smaller fragments will generally find use in hybridization embodiments, wherein the length of the
25 contiguous complementary region may be varied, such as between about 15 and about 100 nucleotides, but larger contiguous complementarity stretches may be used, according to the length complementary sequences one wishes to detect.

The use of a hybridization probe of about 15-25 nucleotides in length allows the formation of a duplex molecule that is both stable and selective. Molecules having

contiguous complementary sequences over stretches greater than 15 bases in length are generally preferred, though, in order to increase stability and selectivity of the hybrid, and thereby improve the quality and degree of specific hybrid molecules obtained. One will generally prefer to design nucleic acid molecules having gene-complementary stretches of
 5 15 to 25 contiguous nucleotides, or even longer where desired.

Hybridization probes may be selected from any portion of any of the sequences disclosed herein. All that is required is to review the sequence set forth in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591,
 10 593-606, 618-705, 709-774, 777, 789, 817, 823 and 824, or to any continuous portion of the sequence, from about 15-25 nucleotides in length up to and including the full length sequence, that one wishes to utilize as a probe or primer. The choice of probe and primer sequences may be governed by various factors. For example, one may wish to employ primers from towards the termini of the total sequence.

15 Small polynucleotide segments or fragments may be readily prepared by, for example, directly synthesizing the fragment by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer. Also, fragments may be obtained by application of nucleic acid reproduction technology, such as the PCR™ technology of U. S. Patent 4,683,202 (incorporated herein by reference), by introducing selected sequences into
 20 recombinant vectors for recombinant production, and by other recombinant DNA techniques generally known to those of skill in the art of molecular biology.

The nucleotide sequences of the invention may be used for their ability to selectively form duplex molecules with complementary stretches of the entire gene or gene fragments of interest. Depending on the application envisioned, one will typically desire to
 25 employ varying conditions of hybridization to achieve varying degrees of selectivity of probe towards target sequence. For applications requiring high selectivity, one will typically desire to employ relatively stringent conditions to form the hybrids, *e.g.*, one will select relatively low salt and/or high temperature conditions, such as provided by a salt concentration of from about 0.02 M to about 0.15 M salt at temperatures of from about

50°C to about 70°C. Such selective conditions tolerate little, if any, mismatch between the probe and the template or target strand, and would be particularly suitable for isolating related sequences.

Of course, for some applications, for example, where one desires to prepare mutants employing a mutant primer strand hybridized to an underlying template, less stringent (reduced stringency) hybridization conditions will typically be needed in order to allow formation of the heteroduplex. In these circumstances, one may desire to employ salt conditions such as those of from about 0.15 M to about 0.9 M salt, at temperatures ranging from about 20°C to about 55°C. Cross-hybridizing species can thereby be readily identified as positively hybridizing signals with respect to control hybridizations. In any case, it is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide, which serves to destabilize the hybrid duplex in the same manner as increased temperature. Thus, hybridization conditions can be readily manipulated, and thus will generally be a method of choice depending on the desired results.

POLYNUCLEOTIDE IDENTIFICATION AND CHARACTERIZATION

Polynucleotides may be identified, prepared and/or manipulated using any of a variety of well established techniques. For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least two fold greater in a tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed, for example, using a Synteni microarray (Palo Alto, CA) according to the manufacturer's instructions (and essentially as described by Schena *et al.*, *Proc. Natl. Acad. Sci. USA* 93:10614-10619, 1996 and Heller *et al.*, *Proc. Natl. Acad. Sci. USA* 94:2150-2155, 1997). Alternatively, polynucleotides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as prostate-specific cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this

approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion of a polynucleotide of the present invention may be used to isolate a full length gene from a suitable library (e.g., a prostate tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with ^{32}P) using well known techniques. A bacterial or bacteriophage library is then generally screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences can then be assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target sequence at temperatures

of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (*see* Triglia *et al.*, *Nucl. Acids Res.* 16:8186, 1988), which uses restriction enzymes to generate a fragment in the
 5 known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the
 10 same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector
 15 sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom *et al.*, *PCR Methods Applic.* 1:111-19, 1991) and walking PCR (Parker *et al.*, *Nucl. Acids. Res.* 19:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by
 20 analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (*e.g.*, NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence. Full length DNA sequences may also be obtained by analysis of genomic fragments.

25 POLYNUCLEOTIDE EXPRESSION IN HOST CELLS

In other embodiments of the invention, polynucleotide sequences or fragments thereof which encode polypeptides of the invention, or fusion proteins or functional equivalents thereof, may be used in recombinant DNA molecules to direct

expression of a polypeptide in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences that encode substantially the same or a functionally equivalent amino acid sequence may be produced and these sequences may be used to clone and express a given polypeptide.

5 As will be understood by those of skill in the art, it may be advantageous in some instances to produce polypeptide-encoding nucleotide sequences possessing non-naturally occurring codons. For example, codons preferred by a particular prokaryotic or eukaryotic host can be selected to increase the rate of protein expression or to produce a recombinant RNA transcript having desirable properties, such as a half-life which is longer
10 than that of a transcript generated from the naturally occurring sequence.

 Moreover, the polynucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter polypeptide encoding sequences for a variety of reasons, including but not limited to, alterations which modify the cloning, processing, and/or expression of the gene product. For example, DNA
15 shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. In addition, site-directed mutagenesis may be used to insert new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, or introduce mutations, and so forth.

20 In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence to encode a fusion protein. For example, to screen peptide libraries for inhibitors of polypeptide activity, it may be useful to encode a chimeric protein that can be recognized by a commercially available antibody. A fusion protein may also be engineered to contain a cleavage site
25 located between the polypeptide-encoding sequence and the heterologous protein sequence, so that the polypeptide may be cleaved and purified away from the heterologous moiety.

 Sequences encoding a desired polypeptide may be synthesized, in whole or in part, using chemical methods well known in the art (see Caruthers, M. H. *et al.* (1980) *Nucl. Acids Res. Symp. Ser.* 215-223, Horn, T. *et al.* (1980) *Nucl. Acids Res. Symp. Ser.*

225-232). Alternatively, the protein itself may be produced using chemical methods to synthesize the amino acid sequence of a polypeptide, or a portion thereof. For example, peptide synthesis can be performed using various solid-phase techniques (Roberge, J. Y. *et al.* (1995) *Science* 269:202-204) and automated synthesis may be achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin Elmer, Palo Alto, CA).

A newly synthesized peptide may be substantially purified by preparative high performance liquid chromatography (*e.g.*, Creighton, T. (1983) *Proteins, Structures and Molecular Principles*, WH Freeman and Co., New York, N.Y.) or other comparable techniques available in the art. The composition of the synthetic peptides may be confirmed by amino acid analysis or sequencing (*e.g.*, the Edman degradation procedure). Additionally, the amino acid sequence of a polypeptide, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

In order to express a desired polypeptide, the nucleotide sequences encoding the polypeptide, or functional equivalents, may be inserted into appropriate expression vector, *i.e.*, a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding a polypeptide of interest and appropriate transcriptional and translational control elements. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. Such techniques are described in Sambrook, J. *et al.* (1989) *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Press, Plainview, N.Y., and Ausubel, F. M. *et al.* (1989) *Current Protocols in Molecular Biology*, John Wiley & Sons, New York. N.Y.

A variety of expression vector/host systems may be utilized to contain and express polynucleotide sequences. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (*e.g.*, baculovirus); plant cell systems transformed

with virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (*e.g.*, Ti or pBR322 plasmids); or animal cell systems.

The "control elements" or "regulatory sequences" present in an expression
 5 vector are those non-translated regions of the vector--enhancers, promoters, 5' and 3' untranslated regions--which interact with host cellular proteins to carry out transcription and translation. Such elements may vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription and translation elements, including constitutive and inducible promoters, may be used. For example, when
 10 cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the PBLUESCRIPT phagemid (Stratagene, La Jolla, Calif.) or PSPORT1 plasmid (Gibco BRL, Gaithersburg, MD) and the like may be used. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses are generally preferred. If it is necessary to generate a cell line that contains multiple copies of the sequence encoding a polypeptide,
 15 vectors based on SV40 or EBV may be advantageously used with an appropriate selectable marker.

In bacterial systems, a number of expression vectors may be selected depending upon the use intended for the expressed polypeptide. For example, when large quantities are needed, for example for the induction of antibodies, vectors which direct
 20 high level expression of fusion proteins that are readily purified may be used. Such vectors include, but are not limited to, the multifunctional *E. coli* cloning and expression vectors such as BLUESCRIPT (Stratagene), in which the sequence encoding the polypeptide of interest may be ligated into the vector in frame with sequences for the amino-terminal Met and the subsequent 7 residues of .beta.-galactosidase so that a hybrid protein is produced;
 25 pIN vectors (Van Heeke, G. and S. M. Schuster (1989) *J. Biol. Chem.* 264:5503-5509); and the like. pGEX Vectors (Promega, Madison, Wis.) may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. Proteins

made in such systems may be designed to include heparin, thrombin, or factor XA protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety at will.

In the yeast, *Saccharomyces cerevisiae*, a number of vectors containing
 5 constitutive or inducible promoters such as alpha factor, alcohol oxidase, and PGH may be used. For reviews, see Ausubel *et al.* (supra) and Grant *et al.* (1987) *Methods Enzymol.* 153:516-544.

In cases where plant expression vectors are used, the expression of
 sequences encoding polypeptides may be driven by any of a number of promoters. For
 10 example, viral promoters such as the 35S and 19S promoters of CaMV may be used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) *EMBO J.* 6:307-311. Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used (Coruzzi, G. *et al.* (1984) *EMBO J.* 3:1671-1680; Broglie, R. *et al.* (1984) *Science* 224:838-843; and Winter, J. *et al.* (1991) *Results Probl.*
 15 *Cell Differ.* 17:85-105). These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. Such techniques are described in a number of generally available reviews (see, for example, Hobbs, S. or Murry, L. E. in McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York, N.Y.; pp. 191-196).

20 An insect system may also be used to express a polypeptide of interest. For example, in one such system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in *Spodoptera frugiperda* cells or in *Trichoplusia* larvae. The sequences encoding the polypeptide may be cloned into a non-essential region of the virus, such as the polyhedrin gene, and placed under control of the
 25 polyhedrin promoter. Successful insertion of the polypeptide-encoding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein. The recombinant viruses may then be used to infect, for example, *S. frugiperda* cells or *Trichoplusia* larvae in which the polypeptide of interest may be expressed (Engelhard, E. K. *et al.* (1994) *Proc. Natl. Acad. Sci.* 91 :3224-3227).

In mammalian host cells, a number of viral-based expression systems are generally available. For example, in cases where an adenovirus is used as an expression vector, sequences encoding a polypeptide of interest may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain a viable virus which is capable of expressing the polypeptide in infected host cells (Logan, J. and Shenk, T. (1984) *Proc. Natl. Acad. Sci.* 81:3655-3659). In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells.

Specific initiation signals may also be used to achieve more efficient translation of sequences encoding a polypeptide of interest. Such signals include the ATG initiation codon and adjacent sequences. In cases where sequences encoding the polypeptide, its initiation codon, and upstream sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a portion thereof, is inserted, exogenous translational control signals including the ATG initiation codon should be provided. Furthermore, the initiation codon should be in the correct reading frame to ensure translation of the entire insert. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers which are appropriate for the particular cell system which is used, such as those described in the literature (Scharf, D. *et al.* (1994) *Results Probl. Cell Differ.* 20:125-162).

In addition, a host cell strain may be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to facilitate correct insertion, folding and/or function. Different host cells such as CHO, HeLa, MDCK, HEK293, and WI38, which have specific cellular machinery and characteristic mechanisms

for such post-translational activities, may be chosen to ensure the correct modification and processing of the foreign protein.

For long-term, high-yield production of recombinant proteins, stable expression is generally preferred. For example, cell lines which stably express a polynucleotide of interest may be transformed using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be proliferated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler, M. *et al.* (1977) *Cell* 11:223-32) and adenine phosphoribosyltransferase (Lowy, I. *et al.* (1990) *Cell* 22:817-23) genes which can be employed in tk.sup.- or aprt.sup.- cells, respectively. Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection; for example, dhfr which confers resistance to methotrexate (Wigler, M. *et al.* (1980) *Proc. Natl. Acad. Sci.* 77:3567-70); npt, which confers resistance to the aminoglycosides, neomycin and G-418 (Colbere-Garapin, F. *et al.* (1981) *J. Mol. Biol.* 150:1-14); and als or pat, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively (Murry, *supra*). Additional selectable genes have been described, for example, trpB, which allows cells to utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine (Hartman, S. C. and R. C. Mulligan (1988) *Proc. Natl. Acad. Sci.* 85:8047-51). Recently, the use of visible markers has gained popularity with such markers as anthocyanins, beta-glucuronidase and its substrate GUS, and luciferase and its substrate luciferin, being widely used not only to identify transformants, but also to quantify the amount of transient or stable protein

expression attributable to a specific vector system (Rhodes, C. A. *et al.* (1995) *Methods Mol. Biol.* 55:121-131).

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, its presence and expression may need to be confirmed. For example, if the sequence encoding a polypeptide is inserted within a marker gene sequence, recombinant cells containing sequences can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a polypeptide-encoding sequence under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

Alternatively, host cells which contain and express a desired polynucleotide sequence may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein.

A variety of protocols for detecting and measuring the expression of polynucleotide-encoded products, using either polyclonal or monoclonal antibodies specific for the product are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on a given polypeptide may be preferred for some applications, but a competitive binding assay may also be employed. These and other assays are described, among other places, in Hampton, R. *et al.* (1990; *Serological Methods, a Laboratory Manual*, APS Press, St Paul, Minn.) and Maddox, D. E. *et al.* (1983; *J. Exp. Med.* 158:1211-1216).

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides include oligolabeling, nick translation, end-labeling or PCR amplification

using a labeled nucleotide. Alternatively, the sequences, or any portions thereof may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled
 5 nucleotides. These procedures may be conducted using a variety of commercially available kits. Suitable reporter molecules or labels, which may be used include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with a polynucleotide sequence of interest may be
 10 cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a recombinant cell may be secreted or contained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides of the invention may be designed to contain signal sequences which direct secretion of the encoded polypeptide
 15 through a prokaryotic or eukaryotic cell membrane. Other recombinant constructions may be used to join sequences encoding a polypeptide of interest to nucleotide sequence encoding a polypeptide domain which will facilitate purification of soluble proteins. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilized metals,
 20 protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp., Seattle, Wash.). The inclusion of cleavable linker sequences such as those specific for Factor XA or enterokinase (Invitrogen, San Diego, Calif.) between the purification domain and the encoded polypeptide may be used to facilitate purification. One such expression vector
 25 provides for expression of a fusion protein containing a polypeptide of interest and a nucleic acid encoding 6 histidine residues preceding a thioredoxin or an enterokinase cleavage site. The histidine residues facilitate purification on IMIAC (immobilized metal ion affinity chromatography) as described in Porath, J. *et al.* (1992, *Prot. Exp. Purif.* 3:263-281) while the enterokinase cleavage site provides a means for purifying the desired

polypeptide from the fusion protein. A discussion of vectors which contain fusion proteins is provided in Kroll, D. J. *et al.* (1993; *DNA Cell Biol.* 12:441-453).

In addition to recombinant production methods, polypeptides of the invention, and fragments thereof, may be produced by direct peptide synthesis using solid-phase techniques (Merrifield J. (1963) *J. Am. Chem. Soc.* 85:2149-2154). Protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Alternatively, various fragments may be chemically synthesized separately and combined using chemical methods to produce the full length molecule.

10 SITE-SPECIFIC MUTAGENESIS

Site-specific mutagenesis is a technique useful in the preparation of individual peptides, or biologically functional equivalent polypeptides, through specific mutagenesis of the underlying polynucleotides that encode them. The technique, well-known to those of skill in the art, further provides a ready ability to prepare and test sequence variants, for example, incorporating one or more of the foregoing considerations, by introducing one or more nucleotide sequence changes into the DNA. Site-specific mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being traversed. Mutations may be employed in a selected polynucleotide sequence to improve, alter, decrease, modify, or otherwise change the properties of the polynucleotide itself, and/or alter the properties, activity, composition, stability, or primary sequence of the encoded polypeptide.

In certain embodiments of the present invention, the inventors contemplate the mutagenesis of the disclosed polynucleotide sequences to alter one or more properties of the encoded polypeptide, such as the antigenicity of a polypeptide vaccine. The techniques of site-specific mutagenesis are well-known in the art, and are widely used to

create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA molecule. In such embodiments, a primer comprising typically about 14 to about 25 nucleotides or so in length is employed, with about 5 to about 10 residues on both sides of the junction of the
 5 sequence being altered.

As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single stranded and double stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage. These phage are readily commercially-available and their use is
 10 generally well-known to those skilled in the art. Double-stranded plasmids are also routinely employed in site directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

In general, site-directed mutagenesis in accordance herewith is performed by first obtaining a single-stranded vector or melting apart of two strands of a
 15 double-stranded vector that includes within its sequence a DNA sequence that encodes the desired peptide. An oligonucleotide primer bearing the desired mutated sequence is prepared, generally synthetically. This primer is then annealed with the single-stranded vector, and subjected to DNA polymerizing enzymes such as *E. coli* polymerase I Klenow fragment, in order to complete the synthesis of the mutation-bearing strand. Thus, a
 20 heteroduplex is formed wherein one strand encodes the original non-mutated sequence and the second strand bears the desired mutation. This heteroduplex vector is then used to transform appropriate cells, such as *E. coli* cells, and clones are selected which include recombinant vectors bearing the mutated sequence arrangement.

The preparation of sequence variants of the selected peptide-encoding DNA
 25 segments using site-directed mutagenesis provides a means of producing potentially useful species and is not meant to be limiting as there are other ways in which sequence variants of peptides and the DNA sequences encoding them may be obtained. For example, recombinant vectors encoding the desired peptide sequence may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants. Specific details regarding

these methods and protocols are found in the teachings of Maloy *et al.*, 1994; Segal, 1976; Prokop and Bajpai, 1991; Kuby, 1994; and Maniatis *et al.*, 1982, each incorporated herein by reference, for that purpose.

As used herein, the term “oligonucleotide directed mutagenesis procedure” refers to template-dependent processes and vector-mediated propagation which result in an increase in the concentration of a specific nucleic acid molecule relative to its initial concentration, or in an increase in the concentration of a detectable signal, such as amplification. As used herein, the term “oligonucleotide directed mutagenesis procedure” is intended to refer to a process that involves the template-dependent extension of a primer molecule. The term template dependent process refers to nucleic acid synthesis of an RNA or a DNA molecule wherein the sequence of the newly synthesized strand of nucleic acid is dictated by the well-known rules of complementary base pairing (see, for example, Watson, 1987). Typically, vector mediated methodologies involve the introduction of the nucleic acid fragment into a DNA or RNA vector, the clonal amplification of the vector, and the recovery of the amplified nucleic acid fragment. Examples of such methodologies are provided by U. S. Patent No. 4,237,224, specifically incorporated herein by reference in its entirety.

POLYNUCLEOTIDE AMPLIFICATION TECHNIQUES

A number of template dependent processes are available to amplify the target sequences of interest present in a sample. One of the best known amplification methods is the polymerase chain reaction (PCRTM) which is described in detail in U.S. Patent Nos. 4,683,195, 4,683,202 and 4,800,159, each of which is incorporated herein by reference in its entirety. Briefly, in PCRTM, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target sequence. An excess of deoxynucleoside triphosphates is added to a reaction mixture along with a DNA polymerase (*e.g.*, *Taq* polymerase). If the target sequence is present in a sample, the primers will bind to the target and the polymerase will cause the primers to be extended along the target sequence by adding on nucleotides. By raising and lowering the

temperature of the reaction mixture, the extended primers will dissociate from the target to form reaction products, excess primers will bind to the target and to the reaction product and the process is repeated. Preferably reverse transcription and PCRTM amplification procedure may be performed in order to quantify the amount of mRNA amplified.

5 Polymerase chain reaction methodologies are well known in the art.

Another method for amplification is the ligase chain reaction (referred to as LCR), disclosed in Eur. Pat. Appl. Publ. No. 320,308 (specifically incorporated herein by reference in its entirety). In LCR, two complementary probe pairs are prepared, and in the presence of the target sequence, each pair will bind to opposite complementary strands of the target such that they abut. In the presence of a ligase, the two probe pairs will link to form a single unit. By temperature cycling, as in PCRTM, bound ligated units dissociate from the target and then serve as "target sequences" for ligation of excess probe pairs. U.S. Patent No. 4,883,750, incorporated herein by reference in its entirety, describes an alternative method of amplification similar to LCR for binding probe pairs to a target sequence.

Qbeta Replicase, described in PCT Intl. Pat. Appl. Publ. No. PCT/US87/00880, incorporated herein by reference in its entirety, may also be used as still another amplification method in the present invention. In this method, a replicative sequence of RNA that has a region complementary to that of a target is added to a sample in the presence of an RNA polymerase. The polymerase will copy the replicative sequence that can then be detected.

An isothermal amplification method, in which restriction endonucleases and ligases are used to achieve the amplification of target molecules that contain nucleotide 5'-[α -thio]triphosphates in one strand of a restriction site (Walker *et al.*, 1992, incorporated herein by reference in its entirety), may also be useful in the amplification of nucleic acids in the present invention.

Strand Displacement Amplification (SDA) is another method of carrying out isothermal amplification of nucleic acids which involves multiple rounds of strand displacement and synthesis, *i.e.* nick translation. A similar method, called Repair Chain

Reaction (RCR) is another method of amplification which may be useful in the present invention and is involves annealing several probes throughout a region targeted for amplification, followed by a repair reaction in which only two of the four bases are present. The other two bases can be added as biotinylated derivatives for easy detection. A similar approach is used in SDA.

Sequences can also be detected using a cyclic probe reaction (CPR). In CPR, a probe having a 3' and 5' sequences of non-target DNA and an internal or "middle" sequence of the target protein specific RNA is hybridized to DNA which is present in a sample. Upon hybridization, the reaction is treated with RNaseH, and the products of the probe are identified as distinctive products by generating a signal that is released after digestion. The original template is annealed to another cycling probe and the reaction is repeated. Thus, CPR involves amplifying a signal generated by hybridization of a probe to a target gene specific expressed nucleic acid.

Still other amplification methods described in Great Britain Pat. Appl. No. 2 02 328, and in PCT Intl. Pat. Appl. Publ. No. PCT/US89/01025, each of which is incorporated herein by reference in its entirety, may be used in accordance with the present invention. In the former application, "modified" primers are used in a PCR-like, template and enzyme dependent synthesis. The primers may be modified by labeling with a capture moiety (*e.g.*, biotin) and/or a detector moiety (*e.g.*, enzyme). In the latter application, an excess of labeled probes is added to a sample. In the presence of the target sequence, the probe binds and is cleaved catalytically. After cleavage, the target sequence is released intact to be bound by excess probe. Cleavage of the labeled probe signals the presence of the target sequence.

Other nucleic acid amplification procedures include transcription-based amplification systems (TAS) (Kwoh *et al.*, 1989; PCT Intl. Pat. Appl. Publ. No. WO 88/10315, incorporated herein by reference in its entirety), including nucleic acid sequence based amplification (NASBA) and 3SR. In NASBA, the nucleic acids can be prepared for amplification by standard phenol/chloroform extraction, heat denaturation of a sample, treatment with lysis buffer and minispin columns for isolation of DNA and RNA or

guanidinium chloride extraction of RNA. These amplification techniques involve annealing a primer that has sequences specific to the target sequence. Following polymerization, DNA/RNA hybrids are digested with RNase H while double stranded DNA molecules are heat-denatured again. In either case the single stranded DNA is made
 5 fully double stranded by addition of second target-specific primer, followed by polymerization. The double stranded DNA molecules are then multiply transcribed by a polymerase such as T7 or SP6. In an isothermal cyclic reaction, the RNAs are reverse transcribed into DNA, and transcribed once again with a polymerase such as T7 or SP6. The resulting products, whether truncated or complete, indicate target-specific sequences.

10 Eur. Pat. Appl. Publ. No. 329,822, incorporated herein by reference in its entirety, disclose a nucleic acid amplification process involving cyclically synthesizing single-stranded RNA ("ssRNA"), ssDNA, and double-stranded DNA (dsDNA), which may be used in accordance with the present invention. The ssRNA is a first template for a first primer oligonucleotide, which is elongated by reverse transcriptase (RNA-dependent DNA
 15 polymerase). The RNA is then removed from resulting DNA:RNA duplex by the action of ribonuclease H (RNase H, an RNase specific for RNA in a duplex with either DNA or RNA). The resultant ssDNA is a second template for a second primer, which also includes the sequences of an RNA polymerase promoter (exemplified by T7 RNA polymerase) 5' to its homology to its template. This primer is then extended by DNA polymerase
 20 (exemplified by the large "Klenow" fragment of *E. coli* DNA polymerase I), resulting as a double-stranded DNA ("dsDNA") molecule, having a sequence identical to that of the original RNA between the primers and having additionally, at one end, a promoter sequence. This promoter sequence can be used by the appropriate RNA polymerase to make many RNA copies of the DNA. These copies can then re-enter the cycle leading to
 25 very swift amplification. With proper choice of enzymes, this amplification can be done isothermally without addition of enzymes at each cycle. Because of the cyclical nature of this process, the starting sequence can be chosen to be in the form of either DNA or RNA.

PCT Intl. Pat. Appl. Publ. No. WO 89/06700, incorporated herein by reference in its entirety, disclose a nucleic acid sequence amplification scheme based on the

hybridization of a promoter/primer sequence to a target single-stranded DNA ("ssDNA") followed by transcription of many RNA copies of the sequence. This scheme is not cyclic; *i.e.* new templates are not produced from the resultant RNA transcripts. Other amplification methods include "RACE" (Frohman, 1990), and "one-sided PCR" (Ohara, 5 1989) which are well-known to those of skill in the art.

Methods based on ligation of two (or more) oligonucleotides in the presence of nucleic acid having the sequence of the resulting "di-oligonucleotide", thereby amplifying the di-oligonucleotide (Wu and Dean, 1996, incorporated herein by reference in its entirety), may also be used in the amplification of DNA sequences of the present 10 invention.

BIOLOGICAL FUNCTIONAL EQUIVALENTS

Modification and changes may be made in the structure of the polynucleotides and polypeptides of the present invention and still obtain a functional molecule that encodes a polypeptide with desirable characteristics. As mentioned above, it 15 is often desirable to introduce one or more mutations into a specific polynucleotide sequence. In certain circumstances, the resulting encoded polypeptide sequence is altered by this mutation, or in other cases, the sequence of the polypeptide is unchanged by one or more mutations in the encoding polynucleotide.

When it is desirable to alter the amino acid sequence of a polypeptide to 20 create an equivalent, or even an improved, second-generation molecule, the amino acid changes may be achieved by changing one or more of the codons of the encoding DNA sequence, according to Table 1.

For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with 25 structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence, and, of course, its underlying DNA coding sequence, and

nevertheless obtain a protein with like properties. It is thus contemplated by the inventors that various changes may be made in the peptide sequences of the disclosed compositions, or corresponding DNA sequences which encode said peptides without appreciable loss of their biological utility or activity.

5

TABLE 1

Amino Acids			Codons						
Alanine	Ala	A	GCA	GCC	GCG	GCU			
Cysteine	Cys	C	UGC	UGU					
Aspartic acid	Asp	D	GAC	GAU					
Glutamic acid	Glu	E	GAA	GAG					
Phenylalanine	Phe	F	UUC	UUU					
Glycine	Gly	G	GGA	GGC	GGG	GGU			
Histidine	His	H	CAC	CAU					
Isoleucine	Ile	I	AUA	AUC	AUU				
Lysine	Lys	K	AAA	AAG					
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU	
Methionine	Met	M	AUG						
Asparagine	Asn	N	AAC	AAU					
Proline	Pro	P	CCA	CCC	CCG	CCU			
Glutamine	Gln	Q	CAA	CAG					
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU	
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU	
Threonine	Thr	T	ACA	ACC	ACG	ACU			
Valine	Val	V	GUA	GUC	GUG	GUU			
Tryptophan	Trp	W	UGG						
Tyrosine	Tyr	Y	UAC	UAU					

In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring interactive

biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982, incorporated herein by reference). It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (−0.4); threonine (−0.7); serine (−0.8); tryptophan (−0.9); tyrosine (−1.3); proline (−1.6); histidine (−3.2); glutamate (−3.5); glutamine (−3.5); aspartate (−3.5); asparagine (−3.5); lysine (−3.9); and arginine (−4.5).

It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a protein with similar biological activity, *i.e.* still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydropathic indices are within ± 2 is preferred, those within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U. S. Patent 4,554,101 (specifically incorporated herein by reference in its entirety), states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein.

As detailed in U. S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 \pm 1); glutamate (+3.0 \pm 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (−0.4); proline (−0.5 \pm 1); alanine (−0.5); histidine (−0.5); cysteine (−1.0); methionine (−1.3); valine (−1.5); leucine (−1.8); isoleucine (−1.8); tyrosine (−2.3); phenylalanine (−2.5); tryptophan (−3.4). It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent, and in particular, an immunologically equivalent protein. In such changes, the

substitution of amino acids whose hydrophilicity values are within ± 2 is preferred, those within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred.

As outlined above, amino acid substitutions are generally therefore based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that take various of the foregoing characteristics into consideration are well known to those of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

In addition, any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl- methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

IN VIVO POLYNUCLEOTIDE DELIVERY TECHNIQUES

In additional embodiments, genetic constructs comprising one or more of the polynucleotides of the invention are introduced into cells *in vivo*. This may be achieved using any of a variety of well known approaches, several of which are outlined below for the purpose of illustration.

1. ADENOVIRUS

One of the preferred methods for *in vivo* delivery of one or more nucleic acid sequences involves the use of an adenovirus expression vector. "Adenovirus expression vector" is meant to include those constructs containing adenovirus sequences sufficient to (a) support packaging of the construct and (b) to express a polynucleotide that has been cloned therein in a sense or antisense orientation. Of course, in the context of an antisense construct, expression does not require that the gene product be synthesized.

The expression vector comprises a genetically engineered form of an adenovirus. Knowledge of the genetic organization of adenovirus, a 36 kb, linear, double-stranded DNA virus, allows substitution of large pieces of adenoviral DNA with foreign sequences up to 7 kb (Grunhaus and Horwitz, 1992). In contrast to retrovirus, the
 5 adenoviral infection of host cells does not result in chromosomal integration because adenoviral DNA can replicate in an episomal manner without potential genotoxicity. Also, adenoviruses are structurally stable, and no genome rearrangement has been detected after extensive amplification. Adenovirus can infect virtually all epithelial cells regardless of their cell cycle stage. So far, adenoviral infection appears to be linked only to mild disease
 10 such as acute respiratory disease in humans.

Adenovirus is particularly suitable for use as a gene transfer vector because of its mid-sized genome, ease of manipulation, high titer, wide target-cell range and high infectivity. Both ends of the viral genome contain 100-200 base pair inverted repeats (ITRs), which are *cis* elements necessary for viral DNA replication and packaging. The
 15 early (E) and late (L) regions of the genome contain different transcription units that are divided by the onset of viral DNA replication. The E1 region (E1A and E1B) encodes proteins responsible for the regulation of transcription of the viral genome and a few cellular genes. The expression of the E2 region (E2A and E2B) results in the synthesis of the proteins for viral DNA replication. These proteins are involved in DNA replication,
 20 late gene expression and host cell shut-off (Renan, 1990). The products of the late genes, including the majority of the viral capsid proteins, are expressed only after significant processing of a single primary transcript issued by the major late promoter (MLP). The MLP, (located at 16.8 m.u.) is particularly efficient during the late phase of infection, and all the mRNA's issued from this promoter possess a 5'-tripartite leader (TPL) sequence
 25 which makes them preferred mRNA's for translation.

In a current system, recombinant adenovirus is generated from homologous recombination between shuttle vector and provirus vector. Due to the possible recombination between two proviral vectors, wild-type adenovirus may be generated from

this process. Therefore, it is critical to isolate a single clone of virus from an individual plaque and examine its genomic structure.

Generation and propagation of the current adenovirus vectors, which are replication deficient, depend on a unique helper cell line, designated 293, which was transformed from human embryonic kidney cells by Ad5 DNA fragments and constitutively expresses E1 proteins (Graham *et al.*, 1977). Since the E3 region is dispensable from the adenovirus genome (Jones and Shenk, 1978), the current adenovirus vectors, with the help of 293 cells, carry foreign DNA in either the E1, the D3 or both regions (Graham and Prevec, 1991). In nature, adenovirus can package approximately 105% of the wild-type genome (Ghosh-Choudhury *et al.*, 1987), providing capacity for about 2 extra kB of DNA. Combined with the approximately 5.5 kB of DNA that is replaceable in the E1 and E3 regions, the maximum capacity of the current adenovirus vector is under 7.5 kB, or about 15% of the total length of the vector. More than 80% of the adenovirus viral genome remains in the vector backbone and is the source of vector-borne cytotoxicity. Also, the replication deficiency of the E1-deleted virus is incomplete. For example, leakage of viral gene expression has been observed with the currently available vectors at high multiplicities of infection (MOI) (Mulligan, 1993).

Helper cell lines may be derived from human cells such as human embryonic kidney cells, muscle cells, hematopoietic cells or other human embryonic mesenchymal or epithelial cells. Alternatively, the helper cells may be derived from the cells of other mammalian species that are permissive for human adenovirus. Such cells include, *e.g.*, Vero cells or other monkey embryonic mesenchymal or epithelial cells. As stated above, the currently preferred helper cell line is 293.

Recently, Racher *et al.* (1995) disclosed improved methods for culturing 293 cells and propagating adenovirus. In one format, natural cell aggregates are grown by inoculating individual cells into 1 liter siliconized spinner flasks (Techne, Cambridge, UK) containing 100-200 ml of medium. Following stirring at 40 rpm, the cell viability is estimated with trypan blue. In another format, Fibra-Cel microcarriers (Bibby Sterlin, Stone, UK) (5 g/l) is employed as follows. A cell inoculum, resuspended in 5 ml of

medium, is added to the carrier (50 ml) in a 250 ml Erlenmeyer flask and left stationary, with occasional agitation, for 1 to 4 h. The medium is then replaced with 50 ml of fresh medium and shaking initiated. For virus production, cells are allowed to grow to about 80% confluence, after which time the medium is replaced (to 25% of the final volume) and
 5 adenovirus added at an MOI of 0.05. Cultures are left stationary overnight, following which the volume is increased to 100% and shaking commenced for another 72 h.

Other than the requirement that the adenovirus vector be replication defective, or at least conditionally defective, the nature of the adenovirus vector is not believed to be crucial to the successful practice of the invention. The adenovirus may be of
 10 any of the 42 different known serotypes or subgroups A-F. Adenovirus type 5 of subgroup C is the preferred starting material in order to obtain a conditional replication-defective adenovirus vector for use in the present invention, since Adenovirus type 5 is a human adenovirus about which a great deal of biochemical and genetic information is known, and it has historically been used for most constructions employing adenovirus as a vector.

15 As stated above, the typical vector according to the present invention is replication defective and will not have an adenovirus E1 region. Thus, it will be most convenient to introduce the polynucleotide encoding the gene of interest at the position from which the E1-coding sequences have been removed. However, the position of insertion of the construct within the adenovirus sequences is not critical to the invention.
 20 The polynucleotide encoding the gene of interest may also be inserted in lieu of the deleted E3 region in E3 replacement vectors as described by Karlsson *et al.* (1986) or in the E4 region where a helper cell line or helper virus complements the E4 defect.

Adenovirus is easy to grow and manipulate and exhibits broad host range *in vitro* and *in vivo*. This group of viruses can be obtained in high titers, *e.g.*, 10^9 - 10^{11} plaque-
 25 forming units per ml, and they are highly infective. The life cycle of adenovirus does not require integration into the host cell genome. The foreign genes delivered by adenovirus vectors are episomal and, therefore, have low genotoxicity to host cells. No side effects have been reported in studies of vaccination with wild-type adenovirus (Couch *et al.*, 1963;

Top *et al.*, 1971), demonstrating their safety and therapeutic potential as *in vivo* gene transfer vectors.

Adenovirus vectors have been used in eukaryotic gene expression (Levrero *et al.*, 1991; Gomez-Foix *et al.*, 1992) and vaccine development (Grunhaus and Horwitz, 1992; Graham and Prevec, 1992). Recently, animal studies suggested that recombinant adenovirus could be used for gene therapy (Stratford-Perricaudet and Perricaudet, 1991; Stratford-Perricaudet *et al.*, 1990; Rich *et al.*, 1993). Studies in administering recombinant adenovirus to different tissues include trachea instillation (Rosenfeld *et al.*, 1991; Rosenfeld *et al.*, 1992), muscle injection (Ragot *et al.*, 1993), peripheral intravenous injections (Herz and Gerard, 1993) and stereotactic inoculation into the brain (Le Gal La Salle *et al.*, 1993).

2. RETROVIRUSES

The retroviruses are a group of single-stranded RNA viruses characterized by an ability to convert their RNA to double-stranded DNA in infected cells by a process of reverse-transcription (Coffin, 1990). The resulting DNA then stably integrates into cellular chromosomes as a provirus and directs synthesis of viral proteins. The integration results in the retention of the viral gene sequences in the recipient cell and its descendants. The retroviral genome contains three genes, gag, pol, and env that code for capsid proteins, polymerase enzyme, and envelope components, respectively. A sequence found upstream from the gag gene contains a signal for packaging of the genome into virions. Two long terminal repeat (LTR) sequences are present at the 5' and 3' ends of the viral genome. These contain strong promoter and enhancer sequences and are also required for integration in the host cell genome (Coffin, 1990).

In order to construct a retroviral vector, a nucleic acid encoding one or more oligonucleotide or polynucleotide sequences of interest is inserted into the viral genome in the place of certain viral sequences to produce a virus that is replication-defective. In order to produce virions, a packaging cell line containing the gag, pol, and env genes but without the LTR and packaging components is constructed (Mann *et al.*, 1983). When a

recombinant plasmid containing a cDNA, together with the retroviral LTR and packaging sequences is introduced into this cell line (by calcium phosphate precipitation for example), the packaging sequence allows the RNA transcript of the recombinant plasmid to be packaged into viral particles, which are then secreted into the culture media (Nicolas and Rubenstein, 1988; Temin, 1986; Mann *et al.*, 1983). The media containing the recombinant retroviruses is then collected, optionally concentrated, and used for gene transfer. Retroviral vectors are able to infect a broad variety of cell types. However, integration and stable expression require the division of host cells (Paskind *et al.*, 1975).

A novel approach designed to allow specific targeting of retrovirus vectors was recently developed based on the chemical modification of a retrovirus by the chemical addition of lactose residues to the viral envelope. This modification could permit the specific infection of hepatocytes *via* sialoglycoprotein receptors.

A different approach to targeting of recombinant retroviruses was designed in which biotinylated antibodies against a retroviral envelope protein and against a specific cell receptor were used. The antibodies were coupled *via* the biotin components by using streptavidin (Roux *et al.*, 1989). Using antibodies against major histocompatibility complex class I and class II antigens, they demonstrated the infection of a variety of human cells that bore those surface antigens with an ecotropic virus *in vitro* (Roux *et al.*, 1989).

3. ADENO-ASSOCIATED VIRUSES

AAV (Ridgeway, 1988; Hermonat and Muzyczka, 1984) is a parovirus, discovered as a contamination of adenoviral stocks. It is a ubiquitous virus (antibodies are present in 85% of the US human population) that has not been linked to any disease. It is also classified as a dependovirus, because its replications is dependent on the presence of a helper virus, such as adenovirus. Five serotypes have been isolated, of which AAV-2 is the best characterized. AAV has a single-stranded linear DNA that is encapsidated into capsid proteins VP1, VP2 and VP3 to form an icosahedral virion of 20 to 24 nm in diameter (Muzyczka and McLaughlin, 1988).

The AAV DNA is approximately 4.7 kilobases long. It contains two open reading frames and is flanked by two ITRs. There are two major genes in the AAV genome: *rep* and *cap*. The *rep* gene codes for proteins responsible for viral replications, whereas *cap* codes for capsid protein VP1-3. Each ITR forms a T-shaped hairpin structure. These terminal repeats are the only essential *cis* components of the AAV for chromosomal integration. Therefore, the AAV can be used as a vector with all viral coding sequences removed and replaced by the cassette of genes for delivery. Three viral promoters have been identified and named p5, p19, and p40, according to their map position. Transcription from p5 and p19 results in production of rep proteins, and transcription from p40 produces the capsid proteins (Hermonat and Muzyczka, 1984).

There are several factors that prompted researchers to study the possibility of using rAAV as an expression vector. One is that the requirements for delivering a gene to integrate into the host chromosome are surprisingly few. It is necessary to have the 145-bp ITRs, which are only 6% of the AAV genome. This leaves room in the vector to assemble a 4.5-kb DNA insertion. While this carrying capacity may prevent the AAV from delivering large genes, it is amply suited for delivering the antisense constructs of the present invention.

AAV is also a good choice of delivery vehicles due to its safety. There is a relatively complicated rescue mechanism: not only wild type adenovirus but also AAV genes are required to mobilize rAAV. Likewise, AAV is not pathogenic and not associated with any disease. The removal of viral coding sequences minimizes immune reactions to viral gene expression, and therefore, rAAV does not evoke an inflammatory response.

4. OTHER VIRAL VECTORS AS EXPRESSION CONSTRUCTS

Other viral vectors may be employed as expression constructs in the present invention for the delivery of oligonucleotide or polynucleotide sequences to a host cell. Vectors derived from viruses such as vaccinia virus (Ridgeway, 1988; Coupar *et al.*, 1988), lentiviruses, polio viruses and herpes viruses may be employed. They offer several

attractive features for various mammalian cells (Friedmann, 1989; Ridgeway, 1988; Coupar *et al.*, 1988; Horwich *et al.*, 1990).

With the recent recognition of defective hepatitis B viruses, new insight was gained into the structure-function relationship of different viral sequences. *In vitro* studies showed that the virus could retain the ability for helper-dependent packaging and reverse transcription despite the deletion of up to 80% of its genome (Horwich *et al.*, 1990). This suggested that large portions of the genome could be replaced with foreign genetic material. The hepatotropism and persistence (integration) were particularly attractive properties for liver-directed gene transfer. Chang *et al.* (1991) introduced the chloramphenicol acetyltransferase (CAT) gene into duck hepatitis B virus genome in the place of the polymerase, surface, and pre-surface coding sequences. It was cotransfected with wild-type virus into an avian hepatoma cell line. Culture media containing high titers of the recombinant virus were used to infect primary duckling hepatocytes. Stable CAT gene expression was detected for at least 24 days after transfection (Chang *et al.*, 1991).

5. NON-VIRAL VECTORS

In order to effect expression of the oligonucleotide or polynucleotide sequences of the present invention, the expression construct must be delivered into a cell. This delivery may be accomplished *in vitro*, as in laboratory procedures for transforming cells lines, or *in vivo* or *ex vivo*, as in the treatment of certain disease states. As described above, one preferred mechanism for delivery is *via* viral infection where the expression construct is encapsulated in an infectious viral particle.

Once the expression construct has been delivered into the cell the nucleic acid encoding the desired oligonucleotide or polynucleotide sequences may be positioned and expressed at different sites. In certain embodiments, the nucleic acid encoding the construct may be stably integrated into the genome of the cell. This integration may be in the specific location and orientation *via* homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation). In yet further embodiments, the nucleic acid may be stably maintained in the cell as a separate, episomal

segment of DNA. Such nucleic acid segments or "episomes" encode sequences sufficient to permit maintenance and replication independent of or in synchronization with the host cell cycle. How the expression construct is delivered to a cell and where in the cell the nucleic acid remains is dependent on the type of expression construct employed.

5 In certain embodiments of the invention, the expression construct comprising one or more oligonucleotide or polynucleotide sequences may simply consist of naked recombinant DNA or plasmids. Transfer of the construct may be performed by any of the methods mentioned above which physically or chemically permeabilize the cell membrane. This is particularly applicable for transfer *in vitro* but it may be applied to *in*
10 *vivo* use as well. Dubensky *et al.* (1984) successfully injected polyomavirus DNA in the form of calcium phosphate precipitates into liver and spleen of adult and newborn mice demonstrating active viral replication and acute infection. Benvenisty and Reshef (1986) also demonstrated that direct intraperitoneal injection of calcium phosphate-precipitated plasmids results in expression of the transfected genes. It is envisioned that DNA encoding
15 a gene of interest may also be transferred in a similar manner *in vivo* and express the gene product.

 Another embodiment of the invention for transferring a naked DNA expression construct into cells may involve particle bombardment. This method depends on the ability to accelerate DNA-coated microprojectiles to a high velocity allowing them
20 to pierce cell membranes and enter cells without killing them (Klein *et al.*, 1987). Several devices for accelerating small particles have been developed. One such device relies on a high voltage discharge to generate an electrical current, which in turn provides the motive force (Yang *et al.*, 1990). The microprojectiles used have consisted of biologically inert substances such as tungsten or gold beads.

25 Selected organs including the liver, skin, and muscle tissue of rats and mice have been bombarded *in vivo* (Yang *et al.*, 1990; Zelenin *et al.*, 1991). This may require surgical exposure of the tissue or cells, to eliminate any intervening tissue between the gun and the target organ, *i.e.* *ex vivo* treatment. Again, DNA encoding a particular gene may be delivered *via* this method and still be incorporated by the present invention.

ANTISENSE OLIGONUCLEOTIDES

The end result of the flow of genetic information is the synthesis of protein. DNA is transcribed by polymerases into messenger RNA and translated on the ribosome to yield a folded, functional protein. Thus there are several steps along the route where protein synthesis can be inhibited. The native DNA segment coding for a polypeptide described herein, as all such mammalian DNA strands, has two strands: a sense strand and an antisense strand held together by hydrogen bonding. The messenger RNA coding for polypeptide has the same nucleotide sequence as the sense DNA strand except that the DNA thymidine is replaced by uridine. Thus, synthetic antisense nucleotide sequences will bind to a mRNA and inhibit expression of the protein encoded by that mRNA.

The targeting of antisense oligonucleotides to mRNA is thus one mechanism to shut down protein synthesis, and, consequently, represents a powerful and targeted therapeutic approach. For example, the synthesis of polygalacturonase and the muscarine type 2 acetylcholine receptor are inhibited by antisense oligonucleotides directed to their respective mRNA sequences (U. S. Patent 5,739,119 and U. S. Patent 5,759,829, each specifically incorporated herein by reference in its entirety). Further, examples of antisense inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1, striatal GABA_A receptor and human EGF (Jaskulski *et al.*, 1988; Vasanthakumar and Ahmed, 1989; Peris *et al.*, 1998; U. S. Patent 5,801,154; U. S. Patent 5,789,573; U. S. Patent 5,718,709 and U. S. Patent 5,610,288, each specifically incorporated herein by reference in its entirety). Antisense constructs have also been described that inhibit and can be used to treat a variety of abnormal cellular proliferations, *e.g.* cancer (U. S. Patent 5,747,470; U. S. Patent 5,591,317 and U. S. Patent 5,783,683, each specifically incorporated herein by reference in its entirety).

Therefore, in exemplary embodiments, the invention provides oligonucleotide sequences that comprise all, or a portion of, any sequence that is capable of specifically binding to polynucleotide sequence described herein, or a complement thereof. In one embodiment, the antisense oligonucleotides comprise DNA or derivatives thereof.

In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a third embodiment, the oligonucleotides are modified DNAs comprising a phosphorothioated modified backbone. In a fourth embodiment, the oligonucleotide sequences comprise peptide nucleic acids or derivatives thereof. In each case, preferred
 5 compositions comprise a sequence region that is complementary, and more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein.

Selection of antisense compositions specific for a given gene sequence is based upon analysis of the chosen target sequence (*i.e.* in these illustrative examples the rat
 10 and human sequences) and determination of secondary structure, T_m , binding energy, relative stability, and antisense compositions were selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce or prohibit specific binding to the target mRNA in a host cell.

Highly preferred target regions of the mRNA, are those which are at or near
 15 the AUG translation initiation codon, and those sequences which were substantially complementary to 5' regions of the mRNA. These secondary structure analyses and target site selection considerations were performed using v.4 of the OLIGO primer analysis software (Rychlik, 1997) and the BLASTN 2.0.5 algorithm software (Altschul *et al.*, 1997).

The use of an antisense delivery method employing a short peptide vector,
 20 termed MPG (27 residues), is also contemplated. The MPG peptide contains a hydrophobic domain derived from the fusion sequence of HIV gp41 and a hydrophilic domain from the nuclear localization sequence of SV40 T-antigen (Morris *et al.*, 1997). It has been demonstrated that several molecules of the MPG peptide coat the antisense oligonucleotides and can be delivered into cultured mammalian cells in less than 1 hour
 25 with relatively high efficiency (90%). Further, the interaction with MPG strongly increases both the stability of the oligonucleotide to nuclease and the ability to cross the plasma membrane (Morris *et al.*, 1997).

RIBOZYMES

Although proteins traditionally have been used for catalysis of nucleic acids, another class of macromolecules has emerged as useful in this endeavor. Ribozymes are RNA-protein complexes that cleave nucleic acids in a site-specific fashion. Ribozymes have specific catalytic domains that possess endonuclease activity (Kim and Cech, 1987; Gerlach *et al.*, 1987; Forster and Symons, 1987). For example, a large number of ribozymes accelerate phosphoester transfer reactions with a high degree of specificity, often cleaving only one of several phosphoesters in an oligonucleotide substrate (Cech *et al.*, 1981; Michel and Westhof, 1990; Reinhold-Hurek and Shub, 1992). This specificity has been attributed to the requirement that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

Ribozyme catalysis has primarily been observed as part of sequence-specific cleavage/ligation reactions involving nucleic acids (Joyce, 1989; Cech *et al.*, 1981). For example, U. S. Patent No. 5,354,855 (specifically incorporated herein by reference) reports that certain ribozymes can act as endonucleases with a sequence specificity greater than that of known ribonucleases and approaching that of the DNA restriction enzymes. Thus, sequence-specific ribozyme-mediated inhibition of gene expression may be particularly suited to therapeutic applications (Scanlon *et al.*, 1991; Sarver *et al.*, 1990). Recently, it was reported that ribozymes elicited genetic changes in some cells lines to which they were applied; the altered genes included the oncogenes H-*ras*, c-*fos* and genes of HIV. Most of this work involved the modification of a target mRNA, based on a specific mutant codon that is cleaved by a specific ribozyme.

Six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds *in trans* (and thus can cleave other RNA molecules) under physiological conditions. In general, enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic

nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it
 5 is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

The enzymatic nature of a ribozyme is advantageous over many technologies, such as antisense technology (where a nucleic acid molecule simply binds to a nucleic acid target to block its translation) since the concentration of ribozyme necessary
 10 to affect a therapeutic treatment is lower than that of an antisense oligonucleotide. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of target RNA. In addition, the ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding to the target RNA, but also on the mechanism of
 15 target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme. Similar mismatches in antisense molecules do not prevent their action (Woolf *et al.*, 1992). Thus, the specificity of action of a ribozyme is greater than that of an antisense oligonucleotide binding the same RNA site.

20 The enzymatic nucleic acid molecule may be formed in a hammerhead, hairpin, a hepatitis δ virus, group I intron or RNaseP RNA (in association with an RNA guide sequence) or Neurospora VS RNA motif. Examples of hammerhead motifs are described by Rossi *et al.* (1992). Examples of hairpin motifs are described by Hampel
 25 *et al.* (Eur. Pat. Appl. Publ. No. EP 0360257), Hampel and Tritz (1989), Hampel *et al.* (1990) and U. S. Patent 5,631,359 (specifically incorporated herein by reference). An example of the hepatitis δ virus motif is described by Perrotta and Been (1992); an example of the RNaseP motif is described by Guerrier-Takada *et al.* (1983); Neurospora VS RNA ribozyme motif is described by Collins (Saville and Collins, 1990; Saville and Collins, 1991; Collins and Olive, 1993); and an example of the Group I intron is described in (U. S.

Patent 4,987,071, specifically incorporated herein by reference). All that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule. Thus the ribozyme constructs need not be limited to specific motifs mentioned herein.

In certain embodiments, it may be important to produce enzymatic cleaving agents which exhibit a high degree of specificity for the RNA of a desired target, such as one of the sequences disclosed herein. The enzymatic nucleic acid molecule is preferably targeted to a highly conserved sequence region of a target mRNA. Such enzymatic nucleic acid molecules can be delivered exogenously to specific cells as required. Alternatively, the ribozymes can be expressed from DNA or RNA vectors that are delivered to specific cells.

Small enzymatic nucleic acid motifs (*e.g.*, of the hammerhead or the hairpin structure) may also be used for exogenous delivery. The simple structure of these molecules increases the ability of the enzymatic nucleic acid to invade targeted regions of the mRNA structure. Alternatively, catalytic RNA molecules can be expressed within cells from eukaryotic promoters (*e.g.*, Scanlon *et al.*, 1991; Kashani-Sabet *et al.*, 1992; Dropulic *et al.*, 1992; Weerasinghe *et al.*, 1991; Ojwang *et al.*, 1992; Chen *et al.*, 1992; Sarver *et al.*, 1990). Those skilled in the art realize that any ribozyme can be expressed in eukaryotic cells from the appropriate DNA vector. The activity of such ribozymes can be augmented by their release from the primary transcript by a second ribozyme (Int. Pat. Appl. Publ. No. WO 93/23569, and Int. Pat. Appl. Publ. No. WO 94/02595, both hereby incorporated by reference; Ohkawa *et al.*, 1992; Taira *et al.*, 1991; and Ventura *et al.*, 1993).

Ribozymes may be added directly, or can be complexed with cationic lipids, lipid complexes, packaged within liposomes, or otherwise delivered to target cells. The RNA or RNA complexes can be locally administered to relevant tissues *ex vivo*, or *in vivo* through injection, aerosol inhalation, infusion pump or stent, with or without their incorporation in biopolymers.

Ribozymes may be designed as described in Int. Pat. Appl. Publ. No. WO 93/23569 and Int. Pat. Appl. Publ. No. WO 94/02595, each specifically incorporated herein by reference) and synthesized to be tested *in vitro* and *in vivo*, as described. Such ribozymes can also be optimized for delivery. While specific examples are provided, those
 5 in the art will recognize that equivalent RNA targets in other species can be utilized when necessary.

Hammerhead or hairpin ribozymes may be individually analyzed by computer folding (Jaeger *et al.*, 1989) to assess whether the ribozyme sequences fold into the appropriate secondary structure. Those ribozymes with unfavorable intramolecular
 10 interactions between the binding arms and the catalytic core are eliminated from consideration. Varying binding arm lengths can be chosen to optimize activity. Generally, at least 5 or so bases on each arm are able to bind to, or otherwise interact with, the target RNA.

Ribozymes of the hammerhead or hairpin motif may be designed to anneal
 15 to various sites in the mRNA message, and can be chemically synthesized. The method of synthesis used follows the procedure for normal RNA synthesis as described in Usman *et al.* (1987) and in Scaringe *et al.* (1990) and makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. Average stepwise coupling yields are typically >98%.
 20 Hairpin ribozymes may be synthesized in two parts and annealed to reconstruct an active ribozyme (Chowrira and Burke, 1992). Ribozymes may be modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-fluoro, 2'-o-methyl, 2'-H (for a review see *e.g.*, Usman and Cedergren, 1992). Ribozymes may be purified by gel electrophoresis using general methods or by high
 25 pressure liquid chromatography and resuspended in water.

Ribozyme activity can be optimized by altering the length of the ribozyme binding arms, or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see *e.g.*, Int. Pat. Appl. Publ. No. WO 92/07065; Perrault *et al.*, 1990; Pieken *et al.*, 1991; Usman and Cedergren, 1992; Int. Pat. Appl. Publ.

No. WO 93/15187; Int. Pat. Appl. Publ. No. WO 91/03162; Eur. Pat. Appl. Publ. No. 92110298.4; U. S. Patent 5,334,711; and Int. Pat. Appl. Publ. No. WO 94/13688, which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules), modifications which enhance their efficacy in cells, and
5 removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

Sullivan *et al.* (Int. Pat. Appl. Publ. No. WO 94/02595) describes the general methods for delivery of enzymatic RNA molecules. Ribozymes may be administered to cells by a variety of methods known to those familiar to the art, including,
10 but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, ribozymes may be directly delivered *ex vivo* to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination may be locally delivered by direct inhalation, by direct injection
15 or by use of a catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of ribozyme delivery and administration are provided in Int. Pat. Appl. Publ. No. WO 94/02595 and Int. Pat. Appl. Publ. No. WO 93/23569, each
20 specifically incorporated herein by reference.

Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozyme-encoding sequences into a DNA expression vector. Transcription of the ribozyme sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III).
25 Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, *etc.*) present nearby. Prokaryotic RNA polymerase promoters may also be used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein and Moss, 1990; Gao and Huang,

1993; Lieber *et al.*, 1993; Zhou *et al.*, 1990). Ribozymes expressed from such promoters can function in mammalian cells (*e.g.* Kashani-Saber *et al.*, 1992; Ojwang *et al.*, 1992; Chen *et al.*, 1992; Yu *et al.*, 1993; L'Huillier *et al.*, 1992; Lisiewicz *et al.*, 1993). Such transcription units can be incorporated into a variety of vectors for introduction into
 5 mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated vectors), or viral RNA vectors (such as retroviral, semliki forest virus, sindbis virus vectors).

Ribozymes may be used as diagnostic tools to examine genetic drift and mutations within diseased cells. They can also be used to assess levels of the target RNA
 10 molecule. The close relationship between ribozyme activity and the structure of the target RNA allows the detection of mutations in any region of the molecule which alters the base-pairing and three-dimensional structure of the target RNA. By using multiple ribozymes, one may map nucleotide changes which are important to RNA structure and function *in vitro*, as well as in cells and tissues. Cleavage of target RNAs with ribozymes may be used
 15 to inhibit gene expression and define the role (essentially) of specified gene products in the progression of disease. In this manner, other genetic targets may be defined as important mediators of the disease. These studies will lead to better treatment of the disease progression by affording the possibility of combinational therapies (*e.g.*, multiple ribozymes targeted to different genes, ribozymes coupled with known small molecule
 20 inhibitors, or intermittent treatment with combinations of ribozymes and/or other chemical or biological molecules). Other *in vitro* uses of ribozymes are well known in the art, and include detection of the presence of mRNA associated with an IL-5 related condition. Such RNA is detected by determining the presence of a cleavage product after treatment with a ribozyme using standard methodology.

25 **PEPTIDE NUCLEIC ACIDS**

In certain embodiments, the inventors contemplate the use of peptide nucleic acids (PNAs) in the practice of the methods of the invention. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and

Nielsen, 1997). PNA is able to be utilized in a number methods that traditionally have used RNA or DNA. Often PNA sequences perform better in techniques than the corresponding RNA or DNA sequences and have utilities that are not inherent to RNA or DNA. A review of PNA including methods of making, characteristics of, and methods of using, is provided
 5 by Corey (1997) and is incorporated herein by reference. As such, in certain embodiments, one may prepare PNA sequences that are complementary to one or more portions of the ACE mRNA sequence, and such PNA compositions may be used to regulate, alter, decrease, or reduce the translation of ACE-specific mRNA, and thereby alter the level of ACE activity in a host cell to which such PNA compositions have been administered.

10 PNAs have 2-aminoethyl-glycine linkages replacing the normal phosphodiester backbone of DNA (Nielsen *et al.*, 1991; Hanvey *et al.*, 1992; Hyrup and Nielsen, 1996; Neilsen, 1996). This chemistry has three important consequences: firstly, in contrast to DNA or phosphorothioate oligonucleotides, PNAs are neutral molecules; secondly, PNAs are achiral, which avoids the need to develop a stereoselective synthesis;
 15 and thirdly, PNA synthesis uses standard Boc (Dueholm *et al.*, 1994) or Fmoc (Thomson *et al.*, 1995) protocols for solid-phase peptide synthesis, although other methods, including a modified Merrifield method, have been used (Christensen *et al.*, 1995).

PNA monomers or ready-made oligomers are commercially available from PerSeptive Biosystems (Framingham, MA). PNA syntheses by either Boc or Fmoc
 20 protocols are straightforward using manual or automated protocols (Norton *et al.*, 1995). The manual protocol lends itself to the production of chemically modified PNAs or the simultaneous synthesis of families of closely related PNAs.

As with peptide synthesis, the success of a particular PNA synthesis will depend on the properties of the chosen sequence. For example, while in theory PNAs can
 25 incorporate any combination of nucleotide bases, the presence of adjacent purines can lead to deletions of one or more residues in the product. In expectation of this difficulty, it is suggested that, in producing PNAs with adjacent purines, one should repeat the coupling of residues likely to be added inefficiently. This should be followed by the purification of PNAs by reverse-phase high-pressure liquid chromatography (Norton *et al.*, 1995)

providing yields and purity of product similar to those observed during the synthesis of peptides.

Modifications of PNAs for a given application may be accomplished by coupling amino acids during solid-phase synthesis or by attaching compounds that contain a carboxylic acid group to the exposed N-terminal amine. Alternatively, PNAs can be modified after synthesis by coupling to an introduced lysine or cysteine. The ease with which PNAs can be modified facilitates optimization for better solubility or for specific functional requirements. Once synthesized, the identity of PNAs and their derivatives can be confirmed by mass spectrometry. Several studies have made and utilized modifications of PNAs (Norton *et al.*, 1995; Haaima *et al.*, 1996; Stetsenko *et al.*, 1996; Petersen *et al.*, 1995; Ulmann *et al.*, 1996; Koch *et al.*, 1995; Orum *et al.*, 1995; Footer *et al.*, 1996; Griffith *et al.*, 1995; Kremsky *et al.*, 1996; Pardridge *et al.*, 1995; Boffa *et al.*, 1995; Landsdorp *et al.*, 1996; Gambacorti-Passerini *et al.*, 1996; Armitage *et al.*, 1997; Seeger *et al.*, 1997; Ruskowski *et al.*, 1997). U.S. Patent No. 5,700,922 discusses PNA-DNA-PNA chimeric molecules and their uses in diagnostics, modulating protein in organisms, and treatment of conditions susceptible to therapeutics.

In contrast to DNA and RNA, which contain negatively charged linkages, the PNA backbone is neutral. In spite of this dramatic alteration, PNAs recognize complementary DNA and RNA by Watson-Crick pairing (Egholm *et al.*, 1993), validating the initial modeling by Nielsen *et al.* (1991). PNAs lack 3' to 5' polarity and can bind in either parallel or antiparallel fashion, with the antiparallel mode being preferred (Egholm *et al.*, 1993).

Hybridization of DNA oligonucleotides to DNA and RNA is destabilized by electrostatic repulsion between the negatively charged phosphate backbones of the complementary strands. By contrast, the absence of charge repulsion in PNA-DNA or PNA-RNA duplexes increases the melting temperature (T_m) and reduces the dependence of T_m on the concentration of mono- or divalent cations (Nielsen *et al.*, 1991). The enhanced rate and affinity of hybridization are significant because they are responsible for the surprising ability of PNAs to perform strand invasion of complementary sequences within

relaxed double-stranded DNA. In addition, the efficient hybridization at inverted repeats suggests that PNAs can recognize secondary structure effectively within double-stranded DNA. Enhanced recognition also occurs with PNAs immobilized on surfaces, and Wang *et al.* have shown that support-bound PNAs can be used to detect hybridization events (Wang
5 *et al.*, 1996).

One might expect that tight binding of PNAs to complementary sequences would also increase binding to similar (but not identical) sequences, reducing the sequence specificity of PNA recognition. As with DNA hybridization, however, selective recognition can be achieved by balancing oligomer length and incubation temperature.
10 Moreover, selective hybridization of PNAs is encouraged by PNA-DNA hybridization being less tolerant of base mismatches than DNA-DNA hybridization. For example, a single mismatch within a 16 bp PNA-DNA duplex can reduce the T_m by up to 15°C (Egholm *et al.*, 1993). This high level of discrimination has allowed the development of several PNA-based strategies for the analysis of point mutations (Wang *et al.*, 1996;
15 Carlsson *et al.*, 1996; Thiede *et al.*, 1996; Webb and Hurskainen, 1996; Perry-O'Keefe *et al.*, 1996).

High-affinity binding provides clear advantages for molecular recognition and the development of new applications for PNAs. For example, 11-13 nucleotide PNAs inhibit the activity of telomerase, a ribonucleo-protein that extends telomere ends using an
20 essential RNA template, while the analogous DNA oligomers do not (Norton *et al.*, 1996).

Neutral PNAs are more hydrophobic than analogous DNA oligomers, and this can lead to difficulty solubilizing them at neutral pH, especially if the PNAs have a high purine content or if they have the potential to form secondary structures. Their solubility can be enhanced by attaching one or more positive charges to the PNA termini
25 (Nielsen *et al.*, 1991).

Findings by Allfrey and colleagues suggest that strand invasion will occur spontaneously at sequences within chromosomal DNA (Boffa *et al.*, 1995; Boffa *et al.*, 1996). These studies targeted PNAs to triplet repeats of the nucleotides CAG and used this recognition to purify transcriptionally active DNA (Boffa *et al.*, 1995) and to inhibit

transcription (Boffa *et al.*, 1996). This result suggests that if PNAs can be delivered within cells then they will have the potential to be general sequence-specific regulators of gene expression. Studies and reviews concerning the use of PNAs as antisense and anti-gene agents include Nielsen *et al.* (1993b), Hanvey *et al.* (1992), and Good and Nielsen (1997).
 5 Koppelhus *et al.* (1997) have used PNAs to inhibit HIV-1 inverse transcription, showing that PNAs may be used for antiviral therapies.

Methods of characterizing the antisense binding properties of PNAs are discussed in Rose (1993) and Jensen *et al.* (1997). Rose uses capillary gel electrophoresis to determine binding of PNAs to their complementary oligonucleotide, measuring the
 10 relative binding kinetics and stoichiometry. Similar types of measurements were made by Jensen *et al.* using BIAcore™ technology.

Other applications of PNAs include use in DNA strand invasion (Nielsen *et al.*, 1991), antisense inhibition (Hanvey *et al.*, 1992), mutational analysis (Orum *et al.*, 1993), enhancers of transcription (Mollegaard *et al.*, 1994), nucleic acid purification (Orum
 15 *et al.*, 1995), isolation of transcriptionally active genes (Boffa *et al.*, 1995), blocking of transcription factor binding (Vickers *et al.*, 1995), genome cleavage (Veselkov *et al.*, 1996), biosensors (Wang *et al.*, 1996), *in situ* hybridization (Thisted *et al.*, 1996), and in a alternative to Southern blotting (Perry-O'Keefe, 1996).

POLYPEPTIDE COMPOSITIONS

20 The present invention, in other aspects, provides polypeptide compositions. Generally, a polypeptide of the invention will be an isolated polypeptide (or an epitope, variant, or active fragment thereof) derived from a mammalian species. Preferably, the polypeptide is encoded by a polynucleotide sequence disclosed herein or a sequence which hybridizes under moderately stringent conditions to a polynucleotide sequence disclosed
 25 herein. Alternatively, the polypeptide may be defined as a polypeptide which comprises a contiguous amino acid sequence from an amino acid sequence disclosed herein, or which polypeptide comprises an entire amino acid sequence disclosed herein.

In the present invention, a polypeptide composition is also understood to comprise one or more polypeptides that are immunologically reactive with antibodies generated against a polypeptide of the invention, particularly a polypeptide having the amino acid sequence disclosed in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 706-708, 775, 776, 778 and 780, or active fragments, variants or biological functional equivalents thereof.

Likewise, a polypeptide composition of the present invention is understood to comprise one or more polypeptides that are capable of eliciting antibodies that are immunologically reactive with one or more polypeptides encoded by one or more contiguous nucleic acid sequences contained in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777, 789, 817, 823 and 824, or to active fragments, or to variants thereof, or to one or more nucleic acid sequences which hybridize to one or more of these sequences under conditions of moderate to high stringency. Particularly illustrative polypeptides include the amino acid sequence disclosed in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 706-708, 775, 776, 778 and 780.

As used herein, an active fragment of a polypeptide includes a whole or a portion of a polypeptide which is modified by conventional techniques, *e.g.*, mutagenesis, or by addition, deletion, or substitution, but which active fragment exhibits substantially the same structure function, antigenicity, etc., as a polypeptide as described herein.

In certain illustrative embodiments, the polypeptides of the invention will comprise at least an immunogenic portion of a prostate-specific protein or a variant thereof, as described herein. As noted above, a "prostate-specific protein" is a protein that is expressed by prostate cells. Proteins that are prostate-specific proteins also react detectably within an immunoassay (such as an ELISA) with antisera from a patient with prostate cancer. Polypeptides as described herein may be of any length. Additional sequences

derived from the native protein and/or heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic properties.

An "immunogenic portion," as used herein is a portion of a protein that is recognized (*i.e.*, specifically bound) by a B-cell and/or T-cell surface antigen receptor.

- 5 Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of a prostate-specific protein or a variant thereof. Certain preferred immunogenic portions include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other preferred immunogenic portions may contain a small N- and/or
- 10 C-terminal deletion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

- Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening
- 15 polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (*i.e.*, they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well known techniques. An
- 20 immunogenic portion of a native prostate-specific protein is a portion that reacts with such antisera and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (*e.g.*, in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length polypeptide. Such screens may generally be performed using
- 25 methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide.

Unbound sera may then be removed and bound antibodies detected using, for example, ¹²⁵I-labeled Protein A.

As noted above, a composition may comprise a variant of a native prostate-specific protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native prostate-specific protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with antigen-specific antisera may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antigen-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

Polypeptide variants encompassed by the present invention include those exhibiting at least about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more identity (determined as described above) to the polypeptides disclosed herein.

Preferably, a variant contains conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine,

isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydrophobic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein, which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (*e.g.*, poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast, and higher eukaryotic cells, such as mammalian cells and plant cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having less than about 100 amino acids, and generally less than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. *See Merrifield, J. Am. Chem. Soc. 85:2149-2146, 1963.* Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused protein, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea *et al.*, *Gene* 40:39-46, 1985; Murphy *et al.*, *Proc. Natl. Acad. Sci. USA* 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided. Such proteins comprise a polypeptide as described herein together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (*see*, for example, Stoute *et al.* *New Engl. J. Med.*, 336:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium *Haemophilus influenza B* (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third

of the protein (e.g., the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in *E. coli* (thus
 5 functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemagglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein
 10 known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the *LytA* gene; *Gene* 43:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to
 15 some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (see *Biotechnology* 10:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A
 20 repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is
 25 isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

BINDING AGENTS

The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to a prostate-specific protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to a prostate-specific protein if it reacts at a detectable level (within, for example, an ELISA) with a prostate-specific protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a complex is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about 10^3 L/mol. The binding constant may be determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as prostate cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a prostate-specific protein will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (*e.g.*, blood, sera, sputum, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an

RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.,* Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In

5 general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (*e.g.,* mice, rats, rabbits, sheep or

10 goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more

15 booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.*

20 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.,* reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell

25 fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection.

After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988) and digested by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ^{90}Y , ^{123}I , ^{125}I , ^{131}I , ^{186}Re , ^{188}Re , ^{211}At , and ^{212}Bi . Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diphtheria toxin, cholera toxin, gelonin, *Pseudomonas* exotoxin, *Shigella* toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (e.g., covalently bonded) to a suitable monoclonal antibody either directly or indirectly (e.g., via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent

capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

5 Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity
10 may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

 It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group.
15 Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell *et al.*

 Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a
20 linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter *et al.*), by hydrolysis of derivatized amino
25 acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn *et al.*), by serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell *et al.*), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler *et al.*).

 It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In

another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers that provide multiple sites for attachment can
 5 be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato *et al.*), peptides and polysaccharides such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih *et al.*). A carrier may also
 10 bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (*e.g.*, U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that
 15 include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison *et al.* discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous,
 20 intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

T CELLS

Immunotherapeutic compositions may also, or alternatively, comprise T
 25 cells specific for a prostate-specific protein. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the Isolex™ System,

available from Nexell Therapeutics, Inc. (Irvine, CA; see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

5 T cells may be stimulated with a prostate-specific polypeptide, polynucleotide encoding a prostate-specific polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, a prostate-specific polypeptide or polynucleotide is present within
10 a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a prostate-specific polypeptide if the T cells specifically proliferate, secrete cytokines or kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium
15 release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen *et al.*, *Cancer Res.* 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by
20 measuring an increased rate of DNA synthesis (*e.g.*, by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a prostate-specific polypeptide (100 ng/ml - 100 µg/ml, preferably 200 ng/ml - 25 µg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in
25 activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (*e.g.*, TNF or IFN-γ) is indicative of T cell activation (*see* Coligan *et al.*, *Current Protocols in Immunology*, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a prostate-specific polypeptide, polynucleotide or polypeptide-expressing APC may be CD4⁺ and/or CD8⁺.

prostate-specific protein-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient, a related donor or an unrelated donor, and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4⁺ or CD8⁺ T cells that proliferate in response to a prostate-specific polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a prostate-specific polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a prostate-specific polypeptide. Alternatively, one or more T cells that proliferate in the presence of a prostate-specific protein can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

PHARMACEUTICAL COMPOSITIONS

In additional embodiments, the present invention concerns formulation of one or more of the polynucleotide, polypeptide, T-cell and/or antibody compositions disclosed herein in pharmaceutically-acceptable solutions for administration to a cell or an animal, either alone, or in combination with one or more other modalities of therapy.

It will also be understood that, if desired, the nucleic acid segment, RNA, DNA or PNA compositions that express a polypeptide as disclosed herein may be administered in combination with other agents as well, such as, *e.g.*, other proteins or polypeptides or various pharmaceutically-active agents. In fact, there is virtually no limit to other components that may also be included, given that the additional agents do not cause a significant adverse effect upon contact with the target cells or host tissues. The compositions may thus be delivered along with various other agents as required in the particular instance. Such compositions may be purified from host cells or other biological sources, or alternatively may be chemically synthesized as described herein. Likewise,

such compositions may further comprise substituted or derivatized RNA or DNA compositions.

Formulation of pharmaceutically-acceptable excipients and carrier solutions is well-known to those of skill in the art, as is the development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including *e.g.*, oral, parenteral, intravenous, intranasal, and intramuscular administration and formulation.

1. ORAL DELIVERY

In certain applications, the pharmaceutical compositions disclosed herein may be delivered *via* oral administration to an animal. As such, these compositions may be formulated with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard- or soft-shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet.

The active compounds may even be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like (Mathiowitz *et al.*, 1997; Hwang *et al.*, 1998; U. S. Patent 5,641,515; U. S. Patent 5,580,579 and U. S. Patent 5,792,451, each specifically incorporated herein by reference in its entirety). The tablets, troches, pills, capsules and the like may also contain the following: a binder, as gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar, or both. A syrup of elixir may contain the active compound sucrose as a sweetening agent methyl and propylparabens as preservatives, a dye and flavoring, such as cherry or orange

flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compounds may be incorporated into sustained-release preparation and formulations.

5 Typically, these formulations may contain at least about 0.1% of the active compound or more, although the percentage of the active ingredient(s) may, of course, be varied and may conveniently be between about 1 or 2% and about 60% or 70% or more of the weight or volume of the total formulation. Naturally, the amount of active compound(s) in each therapeutically useful composition may be prepared in such a way
10 that a suitable dosage will be obtained in any given unit dose of the compound. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

15 For oral administration the compositions of the present invention may alternatively be incorporated with one or more excipients in the form of a mouthwash, dentifrice, buccal tablet, oral spray, or sublingual orally-administered formulation. For example, a mouthwash may be prepared incorporating the active ingredient in the required amount in an appropriate solvent, such as a sodium borate solution (Dobell's Solution).
20 Alternatively, the active ingredient may be incorporated into an oral solution such as one containing sodium borate, glycerin and potassium bicarbonate, or dispersed in a dentifrice, or added in a therapeutically-effective amount to a composition that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants. Alternatively the compositions may be fashioned into a tablet or solution form that may be placed under the
25 tongue or otherwise dissolved in the mouth.

2. INJECTABLE DELIVERY

In certain circumstances it will be desirable to deliver the pharmaceutical compositions disclosed herein parenterally, intravenously, intramuscularly, or even

intraperitoneally as described in U. S. Patent 5,543,158; U. S. Patent 5,641,515 and U. S. Patent 5,399,363 (each specifically incorporated herein by reference in its entirety). Solutions of the active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose.

5 Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile

10 injectable solutions or dispersions (U. S. Patent 5,466,468, specifically incorporated herein by reference in its entirety). In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing,

15 for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be facilitated by various

20 antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

25 For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, a sterile aqueous medium that can be employed will be known to those of

skill in the art in light of the present disclosure. For example, one dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject. Moreover, for human administration, preparations should meet sterility, pyrogenicity, and the general safety and purity standards as required by FDA Office of Biologics standards.

10 Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other
15 ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

The compositions disclosed herein may be formulated in a neutral or salt
20 form. Pharmaceutically-acceptable salts, include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or
25 ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of dosage forms such as injectable solutions, drug-release capsules, and the like.

As used herein, "carrier" includes any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art.

- 5 Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

The phrase "pharmaceutically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when
 10 administered to a human. The preparation of an aqueous composition that contains a protein as an active ingredient is well understood in the art. Typically, such compositions are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection can also be prepared. The preparation can also be emulsified.

15 3. NASAL DELIVERY

In certain embodiments, the pharmaceutical compositions may be delivered by intranasal sprays, inhalation, and/or other aerosol delivery vehicles. Methods for delivering genes, nucleic acids, and peptide compositions directly to the lungs *via* nasal aerosol sprays has been described *e.g.*, in U. S. Patent 5,756,353 and U. S. Patent 5,804,212
 20 (each specifically incorporated herein by reference in its entirety). Likewise, the delivery of drugs using intranasal microparticle resins (Takenaga *et al.*, 1998) and lysophosphatidyl-glycerol compounds (U. S. Patent 5,725,871, specifically incorporated herein by reference in its entirety) are also well-known in the pharmaceutical arts. Likewise, transmucosal drug delivery in the form of a polytetrafluoroethylene support matrix is described in U. S.
 25 Patent 5,780,045 (specifically incorporated herein by reference in its entirety).

4. LIPOSOME-, NANOCAPSULE-, AND MICROPARTICLE-MEDIATED DELIVERY

In certain embodiments, the inventors contemplate the use of liposomes, nanocapsules, microparticles, microspheres, lipid particles, vesicles, and the like, for the introduction of the compositions of the present invention into suitable host cells. In particular, the compositions of the present invention may be formulated for delivery either encapsulated in a lipid particle, a liposome, a vesicle, a nanosphere, or a nanoparticle or the like.

Such formulations may be preferred for the introduction of pharmaceutically-acceptable formulations of the nucleic acids or constructs disclosed herein. The formation and use of liposomes is generally known to those of skill in the art (see for example, Couvreur *et al.*, 1977; Couvreur, 1988; Lasic, 1998; which describes the use of liposomes and nanocapsules in the targeted antibiotic therapy for intracellular bacterial infections and diseases). Recently, liposomes were developed with improved serum stability and circulation half-times (Gabizon and Papahadjopoulos, 1988; Allen and Choun, 1987; U. S. Patent 5,741,516, specifically incorporated herein by reference in its entirety). Further, various methods of liposome and liposome like preparations as potential drug carriers have been reviewed (Takakura, 1998; Chandran *et al.*, 1997; Margalit, 1995; U. S. Patent 5,567,434; U. S. Patent 5,552,157; U. S. Patent 5,565,213; U. S. Patent 5,738,868 and U. S. Patent 5,795,587, each specifically incorporated herein by reference in its entirety).

Liposomes have been used successfully with a number of cell types that are normally resistant to transfection by other procedures including T cell suspensions, primary hepatocyte cultures and PC 12 cells (Renneisen *et al.*, 1990; Muller *et al.*, 1990). In addition, liposomes are free of the DNA length constraints that are typical of viral-based delivery systems. Liposomes have been used effectively to introduce genes, drugs (Heath and Martin, 1986; Heath *et al.*, 1986; Balazsovits *et al.*, 1989; Fresta and Puglisi, 1996), radiotherapeutic agents (Pikul *et al.*, 1987), enzymes (Imaizumi *et al.*, 1990a; Imaizumi *et al.*, 1990b), viruses (Faller and Baltimore, 1984), transcription factors and allosteric effectors (Nicolau and Gersonde, 1979) into a variety of cultured cell lines and animals. In

addition, several successful clinical trials examining the effectiveness of liposome-mediated drug delivery have been completed (Lopez-Berestein *et al.*, 1985a; 1985b; Coune, 1988; Sculier *et al.*, 1988). Furthermore, several studies suggest that the use of liposomes is not associated with autoimmune responses, toxicity or gonadal localization
 5 after systemic delivery (Mori and Fukatsu, 1992).

Liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed multilamellar vesicles (MLVs). MLVs generally have diameters of from 25 nm to 4 μ m. Sonication of MLVs results in the formation of small unilamellar vesicles (SUVs) with
 10 diameters in the range of 200 to 500 Å, containing an aqueous solution in the core.

Liposomes bear resemblance to cellular membranes and are contemplated for use in connection with the present invention as carriers for the peptide compositions. They are widely suitable as both water- and lipid-soluble substances can be entrapped, *i.e.* in the aqueous spaces and within the bilayer itself, respectively. It is possible that the drug-
 15 bearing liposomes may even be employed for site-specific delivery of active agents by selectively modifying the liposomal formulation.

In addition to the teachings of Couvreur *et al.* (1977; 1988), the following information may be utilized in generating liposomal formulations. Phospholipids can form a variety of structures other than liposomes when dispersed in water, depending on the
 20 molar ratio of lipid to water. At low ratios the liposome is the preferred structure. The physical characteristics of liposomes depend on pH, ionic strength and the presence of divalent cations. Liposomes can show low permeability to ionic and polar substances, but at elevated temperatures undergo a phase transition which markedly alters their permeability. The phase transition involves a change from a closely packed, ordered
 25 structure, known as the gel state, to a loosely packed, less-ordered structure, known as the fluid state. This occurs at a characteristic phase-transition temperature and results in an increase in permeability to ions, sugars and drugs.

In addition to temperature, exposure to proteins can alter the permeability of liposomes. Certain soluble proteins, such as cytochrome c, bind, deform and penetrate the

bilayer, thereby causing changes in permeability. Cholesterol inhibits this penetration of proteins, apparently by packing the phospholipids more tightly. It is contemplated that the most useful liposome formations for antibiotic and inhibitor delivery will contain cholesterol.

5 The ability to trap solutes varies between different types of liposomes. For example, MLVs are moderately efficient at trapping solutes, but SUVs are extremely inefficient. SUVs offer the advantage of homogeneity and reproducibility in size distribution, however, and a compromise between size and trapping efficiency is offered by large unilamellar vesicles (LUVs). These are prepared by ether evaporation and are three
10 to four times more efficient at solute entrapment than MLVs.

 In addition to liposome characteristics, an important determinant in entrapping compounds is the physicochemical properties of the compound itself. Polar compounds are trapped in the aqueous spaces and nonpolar compounds bind to the lipid bilayer of the vesicle. Polar compounds are released through permeation or when the
15 bilayer is broken, but nonpolar compounds remain affiliated with the bilayer unless it is disrupted by temperature or exposure to lipoproteins. Both types show maximum efflux rates at the phase transition temperature.

 Liposomes interact with cells *via* four different mechanisms: endocytosis by phagocytic cells of the reticuloendothelial system such as macrophages and neutrophils;
20 adsorption to the cell surface, either by nonspecific weak hydrophobic or electrostatic forces, or by specific interactions with cell-surface components; fusion with the plasma cell membrane by insertion of the lipid bilayer of the liposome into the plasma membrane, with simultaneous release of liposomal contents into the cytoplasm; and by transfer of liposomal
25 lipids to cellular or subcellular membranes, or vice versa, without any association of the liposome contents. It often is difficult to determine which mechanism is operative and more than one may operate at the same time.

 The fate and disposition of intravenously injected liposomes depend on their physical properties, such as size, fluidity, and surface charge. They may persist in tissues for h or days, depending on their composition, and half lives in the blood range from min to

several h. Larger liposomes, such as MLVs and LUVs, are taken up rapidly by phagocytic cells of the reticuloendothelial system, but physiology of the circulatory system restrains the exit of such large species at most sites. They can exit only in places where large openings or pores exist in the capillary endothelium, such as the sinusoids of the liver or spleen. Thus, these organs are the predominate site of uptake. On the other hand, SUVs show a broader tissue distribution but still are sequestered highly in the liver and spleen. In general, this *in vivo* behavior limits the potential targeting of liposomes to only those organs and tissues accessible to their large size. These include the blood, liver, spleen, bone marrow, and lymphoid organs.

Targeting is generally not a limitation in terms of the present invention. However, should specific targeting be desired, methods are available for this to be accomplished. Antibodies may be used to bind to the liposome surface and to direct the antibody and its drug contents to specific antigenic receptors located on a particular cell-type surface. Carbohydrate determinants (glycoprotein or glycolipid cell-surface components that play a role in cell-cell recognition, interaction and adhesion) may also be used as recognition sites as they have potential in directing liposomes to particular cell types. Mostly, it is contemplated that intravenous injection of liposomal preparations would be used, but other routes of administration are also conceivable.

Alternatively, the invention provides for pharmaceutically-acceptable nanocapsule formulations of the compositions of the present invention. Nanocapsules can generally entrap compounds in a stable and reproducible way (Henry-Michelland *et al.*, 1987; Quintanar-Guerrero *et al.*, 1998; Douglas *et al.*, 1987). To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1 μm) should be designed using polymers able to be degraded *in vivo*. Biodegradable polyalkyl-cyanoacrylate nanoparticles that meet these requirements are contemplated for use in the present invention. Such particles may be easily made, as described (Couvreux *et al.*, 1980; 1988; zur Muhlen *et al.*, 1998; Zambaux *et al.* 1998; Pinto-Alphandry *et al.*, 1995 and U. S. Patent 5,145,684, specifically incorporated herein by reference in its entirety).

IMMUNOGENIC COMPOSITIONS

In certain preferred embodiments of the present invention, immunogenic compositions, or vaccines, are provided. The immunogenic compositions will generally comprise one or more pharmaceutical compositions, such as those discussed above, in combination with an immunostimulant. An immunostimulant may be any substance that enhances or potentiates an immune response (antibody and/or cell-mediated) to an exogenous antigen. Examples of immunostimulants include adjuvants, biodegradable microspheres (*e.g.*, polylactic galactide) and liposomes (into which the compound is incorporated; *see e.g.*, Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical compositions and immunogenic compositions within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound, within the composition.

Illustrative immunogenic compositions may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems* 15:143-198, 1998, and references cited therein. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope. In a preferred embodiment, the DNA may be introduced using a viral expression system (*e.g.*, vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for

example, in Fisher-Hoch *et al.*, *Proc. Natl. Acad. Sci. USA* 86:317-321, 1989; Flexner *et al.*, *Ann. N.Y. Acad. Sci.* 569:86-103, 1989; Flexner *et al.*, *Vaccine* 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques* 5 6:616-627, 1988; Rosenfeld *et al.*, *Science* 252:431-434, 1991; Kolls *et al.*, *Proc. Natl. Acad. Sci. USA* 91:215-219, 1994; Kass-Eisler *et al.*, *Proc. Natl. Acad. Sci. USA* 90:11498-11502, 1993; Guzman *et al.*, *Circulation* 88:2838-2848, 1993; and Guzman *et al.*, *Cir. Res.* 73:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be 10 "naked," as described, for example, in Ulmer *et al.*, *Science* 259:1745-1749, 1993 and reviewed by Cohen, *Science* 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells. It will be apparent that an immunogenic composition may comprise both a polynucleotide and a polypeptide component. Such immunogenic compositions may 15 provide for an enhanced immune response.

It will be apparent that an immunogenic composition may contain pharmaceutically acceptable salts of the polynucleotides and polypeptides provided herein. Such salts may be prepared from pharmaceutically acceptable non-toxic bases, including organic bases (*e.g.*, salts of primary, secondary and tertiary amines and basic amino acids) 20 and inorganic bases (*e.g.*, sodium, potassium, lithium, ammonium, calcium and magnesium salts).

While any suitable carrier known to those of ordinary skill in the art may be employed in the compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for 25 any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate,

sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (e.g., polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268; 5,075,109; 5,928,647; 5,811,128; 5,820,883; 5,853,763; 5,814,344 and 5,942,252. One may also employ a carrier comprising the particulate-protein complexes described in U.S. Patent No. 5,928,647, which are capable of inducing a class I-restricted cytotoxic T lymphocyte responses in a host.

Such compositions may also comprise buffers (e.g., neutral buffered saline or phosphate buffered saline), carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, bacteriostats, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum hydroxide), solutes that render the formulation isotonic, hypotonic or weakly hypertonic with the blood of a recipient, suspending agents, thickening agents and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of immunostimulants may be employed in the immunogenic compositions of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bordetella pertussis* or *Mycobacterium tuberculosis* derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); AS-2 (SmithKline Beecham, Philadelphia, PA); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

Within the immunogenic compositions provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (*e.g.*, IFN- γ , TNF α , IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (*e.g.*, IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of an immunogenic composition as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, *Ann. Rev. Immunol.* 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Corixa Corporation (Seattle, WA; *see* US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Patent Nos. 6,008,200 and 5,856,462. Immunostimulatory DNA sequences are also described, for example, by Sato *et al.*, *Science* 273:352, 1996. Another preferred adjuvant is a saponin, preferably QS21 (Aquila Biopharmaceuticals Inc., Framingham, MA), which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprise an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210.

Other preferred adjuvants include Montanide ISA 720 (Seppic, France), SAF (Chiron, California, United States), ISCOMS (CSL), MF-59 (Chiron), the SBAS series of adjuvants (*e.g.*, SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart, Belgium), Detox (Corixa, Hamilton, MT), RC-529 (Corixa, Hamilton, MT) and
 5 other aminoalkyl glucosaminide 4-phosphates (AGPs), such as those described in pending U.S. Patent Application Serial Nos. 08/853,826 and 09/074,720, the disclosures of which are incorporated herein by reference in their entireties.

Any immunogenic composition provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a
 10 suitable carrier or excipient. The compositions described herein may be administered as part of a sustained release formulation (*i.e.*, a formulation such as a capsule, sponge or gel (composed of polysaccharides, for example) that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology (*see, e.g.*, Coombes *et al.*, *Vaccine* 14:1429-1438, 1996) and administered by,
 15 for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane.

Carriers for use within such formulations are biocompatible, and may also
 20 be biodegradable; preferably the formulation provides a relatively constant level of active component release. Such carriers include microparticles of poly(lactide-co-glycolide), polyacrylate, latex, starch, cellulose, dextran and the like. Other delayed-release carriers include supramolecular biovectors, which comprise a non-liquid hydrophilic core (*e.g.*, a cross-linked polysaccharide or oligosaccharide) and, optionally, an external layer
 25 comprising an amphiphilic compound, such as a phospholipid (*see e.g.*, U.S. Patent No. 5,151,254 and PCT applications WO 94/20078, WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and immunogenic compositions to facilitate production of an antigen-specific immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature* 392:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med.* 50:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up, process and present antigens with high efficiency and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within an immunogenic composition (*see* Zitvogel *et al.*, *Nature Med.* 4:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4,

IL-13 and/or TNF α to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNF α , CD40 ligand, LPS, flt3 ligand and/or other
 5 compound(s) that induce differentiation, maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC
 10 with a high capacity for antigen uptake and processing, which correlates with the high expression of Fc γ receptor and mannose receptor. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (*e.g.*, CD54 and CD11) and costimulatory molecules (*e.g.*, CD40, CD80, CD86
 15 and 4-1BB).

APCs may generally be transfected with a polynucleotide encoding a prostate-specific protein (or portion or other variant thereof) such that the prostate-specific polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place *ex vivo*, and a composition comprising such transfected cells
 20 may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs *in vivo*. *In vivo* and *ex vivo* transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach
 25 described by Mahvi *et al.*, *Immunology and cell Biology* 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the prostate-specific polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (*e.g.*, vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently

conjugated to an immunological partner that provides T cell help (*e.g.*, a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

Immunogenic compositions and pharmaceutical compositions may be presented in unit-dose or multi-dose containers, such as sealed ampoules or vials. Such containers are preferably hermetically sealed to preserve sterility of the formulation until use. In general, formulations may be stored as suspensions, solutions or emulsions in oily or aqueous vehicles. Alternatively, a immunogenic composition or pharmaceutical composition may be stored in a freeze-dried condition requiring only the addition of a sterile liquid carrier immediately prior to use.

CANCER THERAPY

In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as prostate cancer. Within such methods, pharmaceutical compositions and immunogenic compositions are typically administered to a patient. As used herein, a “patient” refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and immunogenic compositions may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. A cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and immunogenic compositions may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs. Administration may be by any suitable method, including administration by intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal, intradermal, anal, vaginal, topical and oral routes.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host

immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides as provided herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as CD8⁺ cytotoxic T lymphocytes and CD4⁺ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast and/or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*.

Studies have shown that cultured effector cells can be induced to grow *in vivo* and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (*see, for example, Cheever et al., Immunological Reviews 157:177, 1997*).

5 Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

10 Routes and frequency of administration of the therapeutic compositions described herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and immunogenic compositions may be administered by injection (*e.g., intracutaneous, intramuscular, intravenous or subcutaneous*), intranasally (*e.g., by aspiration*) or orally.

15 Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50%

20 above the basal (*i.e., untreated*) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells *in vitro*. Such immunogenic compositions should also be capable of causing an immune response that leads to an improved clinical outcome (*e.g., more frequent remissions, complete or partial or longer disease-free*

25 survival) in treated patients as compared to non-treated patients. In general, for pharmaceutical compositions and immunogenic compositions comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a prostate-specific protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

10 CANCER DETECTION AND DIAGNOSIS

In general, a cancer may be detected in a patient based on the presence of one or more prostate-specific proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, sputum urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as prostate cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a prostate-specific sequence should be present at a level that is at least three fold higher in prostate tissue than in other normal tissues.

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex.

5 Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent

10 with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length prostate-specific proteins and portions thereof to which the binding agent binds, as described above.

15 The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic

20 particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which

25 may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1

hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 μ g, and preferably about 100 ng to about 1 μ g, is sufficient to immobilize an adequate amount of binding agent.

5 Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group
10 on the support with an amine and an active hydrogen on the binding partner (*see, e.g.*, Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that
15 polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the
20 specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20TM (Sigma Chemical Co., St. Louis, MO). The immobilized
25 antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with prostate cancer. Preferably, the contact time is

sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as prostate cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver

Operator Curve, according to the method of Sackett *et al.*, *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of

antibody immobilized on the membrane ranges from about 25 ng to about 1 μ g, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use prostate-specific polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such prostate-specific protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a prostate-specific protein in a biological sample. Within certain methods, a biological sample comprising CD4⁺ and/or CD8⁺ T cells isolated from a patient is incubated with a prostate-specific polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated *in vitro* for 2-9 days (typically 4 days) at 37°C with polypeptide (*e.g.*, 5 - 25 μ g/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of prostate-specific polypeptide to serve as a control. For CD4⁺ T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8⁺ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a prostate-specific protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction

(PCR) based assay to amplify a portion of a prostate-specific cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the prostate-specific protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a prostate-specific protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a prostate-specific protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777, 789, 817, 823 and 824. Techniques for both PCR based assays and hybridization assays are well known in the art (*see*, for example, Mullis *et al.*, *Cold Spring Harbor Symp. Quant. Biol.*, 51:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is

not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

5 In another embodiment, the compositions described herein may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed
10 as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor.
15 One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple prostate-specific protein
20 markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins
25 provided herein may be combined with assays for other known tumor antigens.

DIAGNOSTIC KITS

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for

performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a prostate-specific protein. Such antibodies or fragments may be provided attached to a support material, as described
5 above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a
10 prostate-specific protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a prostate-specific protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to
15 facilitate the detection of a polynucleotide encoding a prostate-specific protein.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLE 1

ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC POLYPEPTIDES

This Example describes the isolation of certain prostate-specific
 5 polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library was constructed from prostate tumor poly A⁺ RNA using a Superscript Plasmid System for cDNA Synthesis and Plasmid Cloning kit (BRL Life Technologies, Gaithersburg, MD 20897) following the manufacturer's protocol. Specifically, prostate tumor tissues were homogenized with
 10 polytron (Kinematica, Switzerland) and total RNA was extracted using Trizol reagent (BRL Life Technologies) as directed by the manufacturer. The poly A⁺ RNA was then purified using a Qiagen oligotex spin column mRNA purification kit (Qiagen, Santa Clarita, CA 91355) according to the manufacturer's protocol. First-strand cDNA was synthesized using the NotI/Oligo-dT18 primer. Double-stranded cDNA was synthesized,
 15 ligated with EcoRI/BAXI adaptors (Invitrogen, San Diego, CA) and digested with NotI. Following size fractionation with Chroma Spin-1000 columns (Clontech, Palo Alto, CA), the cDNA was ligated into the EcoRI/NotI site of pCDNA3.1 (Invitrogen) and transformed into ElectroMax *E. coli* DH10B cells (BRL Life Technologies) by electroporation.

Using the same procedure, a normal human pancreas cDNA expression
 20 library was prepared from a pool of six tissue specimens (Clontech). The cDNA libraries were characterized by determining the number of independent colonies, the percentage of clones that carried insert, the average insert size and by sequence analysis. The prostate tumor library contained 1.64×10^7 independent colonies, with 70% of clones having an insert and the average insert size being 1745 base pairs. The normal pancreas cDNA
 25 library contained 3.3×10^6 independent colonies, with 69% of clones having inserts and the average insert size being 1120 base pairs. For both libraries, sequence analysis showed that the majority of clones had a full length cDNA sequence and were synthesized from mRNA, with minimal rRNA and mitochondrial DNA contamination.

cDNA library subtraction was performed using the above prostate tumor and normal pancreas cDNA libraries, as described by Hara *et al.* (*Blood*, 84:189-199, 1994) with some modifications. Specifically, a prostate tumor-specific subtracted cDNA library was generated as follows. Normal pancreas cDNA library (70 µg) was digested with
 5 EcoRI, NotI, and SfuI, followed by a filling-in reaction with DNA polymerase Klenow fragment. After phenol-chloroform extraction and ethanol precipitation, the DNA was dissolved in 100 µl of H₂O, heat-denatured and mixed with 100 µl (100 µg) of Photoprobe biotin (Vector Laboratories, Burlingame, CA). As recommended by the manufacturer, the resulting mixture was irradiated with a 270 W sunlamp on ice for 20 minutes. Additional
 10 Photoprobe biotin (50 µl) was added and the biotinylation reaction was repeated. After extraction with butanol five times, the DNA was ethanol-precipitated and dissolved in 23 µl H₂O to form the driver DNA.

To form the tracer DNA, 10 µg prostate tumor cDNA library was digested with BamHI and XhoI, phenol chloroform extracted and passed through Chroma spin-400
 15 columns (Clontech). Following ethanol precipitation, the tracer DNA was dissolved in 5 µl H₂O. Tracer DNA was mixed with 15 µl driver DNA and 20 µl of 2 x hybridization buffer (1.5 M NaCl/10 mM EDTA/50 mM HEPES pH 7.5/0.2% sodium dodecyl sulfate), overlaid with mineral oil, and heat-denatured completely. The sample was immediately transferred into a 68 °C water bath and incubated for 20 hours (long hybridization [LH]). The reaction
 20 mixture was then subjected to a streptavidin treatment followed by phenol/chloroform extraction. This process was repeated three more times. Subtracted DNA was precipitated, dissolved in 12 µl H₂O, mixed with 8 µl driver DNA and 20 µl of 2 x hybridization buffer, and subjected to a hybridization at 68 °C for 2 hours (short hybridization [SH]). After removal of biotinylated double-stranded DNA, subtracted cDNA was ligated into
 25 BamHI/XhoI site of chloramphenicol resistant pBCSK⁺ (Stratagene, La Jolla, CA 92037) and transformed into ElectroMax *E. coli* DH10B cells by electroporation to generate a prostate tumor specific subtracted cDNA library (referred to as “prostate subtraction 1”).

To analyze the subtracted cDNA library, plasmid DNA was prepared from 100 independent clones, randomly picked from the subtracted prostate tumor specific

library and grouped based on insert size. Representative cDNA clones were further characterized by DNA sequencing with a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A (Foster City, CA). Six cDNA clones, hereinafter referred to as F1-13, F1-12, F1-16, H1-1, H1-9 and H1-4, were shown to be abundant in the subtracted prostate-specific cDNA library. The determined 3' and 5' cDNA sequences for F1-12 are provided in SEQ ID NO: 2 and 3, respectively, with determined 3' cDNA sequences for F1-13, F1-16, H1-1, H1-9 and H1-4 being provided in SEQ ID NO: 1 and 4-7, respectively.

The cDNA sequences for the isolated clones were compared to known sequences in the gene bank using the EMBL and GenBank databases (release 96). Four of the prostate tumor cDNA clones, F1-13, F1-16, H1-1, and H1-4, were determined to encode the following previously identified proteins: prostate specific antigen (PSA), human glandular kallikrein, human tumor expression enhanced gene, and mitochondria cytochrome C oxidase subunit II. H1-9 was found to be identical to a previously identified human autonomously replicating sequence. No significant homologies to the cDNA sequence for F1-12 were found.

Subsequent studies led to the isolation of a full-length cDNA sequence for F1-12 (also referred to as P504S). This sequence is provided in SEQ ID NO: 107, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 108. cDNA splice variants of P504S are provided in SEQ ID NO: 600-605.

To clone less abundant prostate tumor specific genes, cDNA library subtraction was performed by subtracting the prostate tumor cDNA library described above with the normal pancreas cDNA library and with the three most abundant genes in the previously subtracted prostate tumor specific cDNA library: human glandular kallikrein, prostate specific antigen (PSA), and mitochondria cytochrome C oxidase subunit II. Specifically, 1 μ g each of human glandular kallikrein, PSA and mitochondria cytochrome C oxidase subunit II cDNAs in pCDNA3.1 were added to the driver DNA and subtraction was performed as described above to provide a second subtracted cDNA library hereinafter referred to as the "subtracted prostate tumor specific cDNA library with spike".

Twenty-two cDNA clones were isolated from the subtracted prostate tumor specific cDNA library with spike. The determined 3' and 5' cDNA sequences for the clones referred to as J1-17, L1-12, N1-1862, J1-13, J1-19, J1-25, J1-24, K1-58, K1-63, L1-4 and L1-14 are provided in SEQ ID NOS: 8-9, 10-11, 12-13, 14-15, 16-17, 18-19, 20-21, 22-23, 24-25, 26-27 and 28-29, respectively. The determined 3' cDNA sequences for the clones referred to as J1-12, J1-16, J1-21, K1-48, K1-55, L1-2, L1-6, N1-1858, N1-1860, N1-1861, N1-1864 are provided in SEQ ID NOS: 30-40, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to three of the five most abundant DNA species, (J1-17, L1-12 and N1-1862; SEQ ID NOS: 8-9, 10-11 and 12-13, respectively). Of the remaining two most abundant species, one (J1-12; SEQ ID NO:30) was found to be identical to the previously identified human pulmonary surfactant-associated protein, and the other (K1-48; SEQ ID NO:33) was determined to have some homology to *R. norvegicus* mRNA for 2-arylpropionyl-CoA epimerase. Of the 17 less abundant cDNA clones isolated from the subtracted prostate tumor specific cDNA library with spike, four (J1-16, K1-55, L1-6 and N1-1864; SEQ ID NOS:31, 34, 36 and 40, respectively) were found to be identical to previously identified sequences, two (J1-21 and N1-1860; SEQ ID NOS: 32 and 38, respectively) were found to show some homology to non-human sequences, and two (L1-2 and N1-1861; SEQ ID NOS: 35 and 39, respectively) were found to show some homology to known human sequences. No significant homologies were found to the polypeptides J1-13, J1-19, J1-24, J1-25, K1-58, K1-63, L1-4, L1-14 (SEQ ID NOS: 14-15, 16-17, 20-21, 18-19, 22-23, 24-25, 26-27, 28-29, respectively).

Subsequent studies led to the isolation of full length cDNA sequences for J1-17, L1-12 and N1-1862 (SEQ ID NOS: 109-111, respectively). The corresponding predicted amino acid sequences are provided in SEQ ID NOS: 112-114. L1-12 is also referred to as P501S. A cDNA splice variant of P501S is provided in SEQ ID NO: 606.

In a further experiment, four additional clones were identified by subtracting a prostate tumor cDNA library with normal prostate cDNA prepared from a pool of three normal prostate poly A⁺ RNA (referred to as "prostate subtraction 2"). The determined

cDNA sequences for these clones, hereinafter referred to as U1-3064, U1-3065, V1-3692 and 1A-3905, are provided in SEQ ID NO: 69-72, respectively. Comparison of the determined sequences with those in the gene bank revealed no significant homologies to U1-3065.

5 A second subtraction with spike (referred to as “prostate subtraction spike 2”) was performed by subtracting a prostate tumor specific cDNA library with spike with normal pancreas cDNA library and further spiked with PSA, J1-17, pulmonary surfactant-associated protein, mitochondrial DNA, cytochrome c oxidase subunit II, N1-1862, autonomously replicating sequence, L1-12 and tumor expression enhanced gene. Four
10 additional clones, hereinafter referred to as V1-3686, R1-2330, 1B-3976 and V1-3679, were isolated. The determined cDNA sequences for these clones are provided in SEQ ID NO:73-76, respectively. Comparison of these sequences with those in the gene bank revealed no significant homologies to V1-3686 and R1-2330.

Further analysis of the three prostate subtractions described above (prostate
15 subtraction 2, subtracted prostate tumor specific cDNA library with spike, and prostate subtraction spike 2) resulted in the identification of sixteen additional clones, referred to as 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1G-4734, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4810, 1I-4811, 1J-4876, 1K-4884 and 1K-4896. The determined cDNA sequences for these clones are provided in SEQ ID NOS: 77-92, respectively. Comparison
20 of these sequences with those in the gene bank as described above, revealed no significant homologies to 1G-4741, 1G-4734, 1I-4807, 1J-4876 and 1K-4896 (SEQ ID NOS: 79, 81, 87, 90 and 92, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4807, 1J-4876, 1K-4884 and 1K-
25 4896, provided in SEQ ID NOS: 179-188 and 191-193, respectively, and to the determination of additional partial cDNA sequences for 1I-4810 and 1I-4811, provided in SEQ ID NOS: 189 and 190, respectively.

Additional studies with prostate subtraction spike 2 resulted in the isolation of three more clones. Their sequences were determined as described above and compared

to the most recent GenBank. All three clones were found to have homology to known genes, which are Cysteine-rich protein, KIAA0242, and KIAA0280 (SEQ ID NO: 317, 319, and 320, respectively). Further analysis of these clones by Synteni microarray (Synteni, Palo Alto, CA) demonstrated that all three clones were over-expressed in most prostate tumors and prostate BPH, as well as in the majority of normal prostate tissues tested, but low expression in all other normal tissues.

An additional subtraction was performed by subtracting a normal prostate cDNA library with normal pancreas cDNA (referred to as "prostate subtraction 3"). This led to the identification of six additional clones referred to as 1G-4761, 1G-4762, 1H-4766, 1H-4770, 1H-4771 and 1H-4772 (SEQ ID NOS: 93-98). Comparison of these sequences with those in the gene bank revealed no significant homologies to 1G-4761 and 1H-4771 (SEQ ID NOS: 93 and 97, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1G-4761, 1G-4762, 1H-4766 and 1H-4772 provided in SEQ ID NOS: 194-196 and 199, respectively, and to the determination of additional partial cDNA sequences for 1H-4770 and 1H-4771, provided in SEQ ID NOS: 197 and 198, respectively.

Subtraction of a prostate tumor cDNA library, prepared from a pool of polyA⁺ RNA from three prostate cancer patients, with a normal pancreas cDNA library (prostate subtraction 4) led to the identification of eight clones, referred to as 1D-4297, 1D-4309, 1D-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280 (SEQ ID NOS: 99-107). These sequences were compared to those in the gene bank as described above. No significant homologies were found to 1D-4283 and 1D-4304 (SEQ ID NOS: 103 and 104, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1D-4309, 1D-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280, provided in SEQ ID NOS: 200-206, respectively.

cDNA clones isolated in prostate subtraction 1 and prostate subtraction 2, described above, were colony PCR amplified and their mRNA expression levels in prostate tumor, normal prostate and in various other normal tissues were determined using microarray technology (Synteni, Palo Alto, CA). Briefly, the PCR amplification products

were dotted onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, reverse transcribed, and fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured.

5 This intensity correlates with the hybridization intensity. Two clones (referred to as P509S and P510S) were found to be over-expressed in prostate tumor and normal prostate and expressed at low levels in all other normal tissues tested (liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon). The determined cDNA sequences for

10 P509S and P510S are provided in SEQ ID NO: 223 and 224, respectively. Comparison of these sequences with those in the gene bank as described above, revealed some homology to previously identified ESTs.

Additional, studies led to the isolation of the full-length cDNA sequence for P509S. This sequence is provided in SEQ ID NO: 332, with the corresponding predicted

15 amino acid sequence being provided in SEQ ID NO: 339. Two variant full-length cDNA sequences for P510S are provided in SEQ ID NO: 535 and 536, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 537 and 538, respectively. Additional splice variants of P510S are provided in SEQ ID NO: 598 and 599.

The determined cDNA sequences for additional prostate-specific clones

20 isolated during characterization of prostate specific cDNA libraries are provided in SEQ ID NO: 618-689, 691-697 and 709-772. Comparison of these sequences with those in the public databases revealed no significant homologies to any of these sequences.

EXAMPLE 2

25 DETERMINATION OF TISSUE SPECIFICITY OF PROSTATE-SPECIFIC POLYPEPTIDES

Using gene specific primers, mRNA expression levels for the representative prostate-specific polypeptides F1-16, H1-1, J1-17 (also referred to as P502S), L1-12 (also

referred to as P501S), F1-12 (also referred to as P504S) and N1-1862 (also referred to as P503S) were examined in a variety of normal and tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor tissues using Trizol reagent as described above. First strand synthesis was carried out using 1-2
 5 μ g of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42 °C for one hour. The cDNA was then amplified by PCR with gene-specific primers. To ensure the semi-quantitative nature of the RT-PCR, β -actin was used as an internal control for each of the tissues examined. First, serial dilutions of the first strand cDNAs were prepared and RT-PCR assays were performed using β -actin specific primers. A dilution
 10 was then chosen that enabled the linear range amplification of the β -actin template and which was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the β -actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding
 15 reverse transcriptase.

mRNA Expression levels were examined in four different types of tumor tissue (prostate tumor from 2 patients, breast tumor from 3 patients, colon tumor, lung tumor), and sixteen different normal tissues, including prostate, colon, kidney, liver, lung, ovary, pancreas, skeletal muscle, skin, stomach, testes, bone marrow and brain. F1-16 was
 20 found to be expressed at high levels in prostate tumor tissue, colon tumor and normal prostate, and at lower levels in normal liver, skin and testes, with expression being undetectable in the other tissues examined. H1-1 was found to be expressed at high levels in prostate tumor, lung tumor, breast tumor, normal prostate, normal colon and normal brain, at much lower levels in normal lung, pancreas, skeletal muscle, skin, small intestine,
 25 bone marrow, and was not detected in the other tissues tested. J1-17 (P502S) and L1-12 (P501S) appear to be specifically over-expressed in prostate, with both genes being expressed at high levels in prostate tumor and normal prostate but at low to undetectable levels in all the other tissues examined. N1-1862 (P503S) was found to be over-expressed in 60% of prostate tumors and detectable in normal colon and kidney. The RT-PCR results

thus indicate that F1-16, H1-1, J1-17 (P502S), N1-1862 (P503S) and L1-12 (P501S) are either prostate specific or are expressed at significantly elevated levels in prostate.

Further RT-PCR studies showed that F1-12 (P504S) is over-expressed in 60% of prostate tumors, detectable in normal kidney but not detectable in all other tissues tested. Similarly, R1-2330 was shown to be over-expressed in 40% of prostate tumors, detectable in normal kidney and liver, but not detectable in all other tissues tested. U1-3064 was found to be over-expressed in 60% of prostate tumors, and also expressed in breast and colon tumors, but was not detectable in normal tissues.

RT-PCR characterization of R1-2330, U1-3064 and 1D-4279 showed that these three antigens are over-expressed in prostate and/or prostate tumors.

Northern analysis with four prostate tumors, two normal prostate samples, two BPH prostates, and normal colon, kidney, liver, lung, pancreas, skeletal muscle, brain, stomach, testes, small intestine and bone marrow, showed that L1-12 (P501S) is over-expressed in prostate tumors and normal prostate, while being undetectable in other normal tissues tested. J1-17 (P502S) was detected in two prostate tumors and not in the other tissues tested. N1-1862 (P503S) was found to be over-expressed in three prostate tumors and to be expressed in normal prostate, colon and kidney, but not in other tissues tested. F1-12 (P504S) was found to be highly expressed in two prostate tumors and to be undetectable in all other tissues tested.

The microarray technology described above was used to determine the expression levels of representative antigens described herein in prostate tumor, breast tumor and the following normal tissues: prostate, liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon. L1-12 (P501S) was found to be over-expressed in normal prostate and prostate tumor, with some expression being detected in normal skeletal muscle. Both J1-12 and F1-12 (P504S) were found to be over-expressed in prostate tumor, with expression being lower or undetectable in all other tissues tested. N1-1862 (P503S) was found to be expressed at high levels in prostate tumor and normal prostate, and at low levels in normal large intestine and normal colon, with expression

being undetectable in all other tissues tested. R1-2330 was found to be over-expressed in prostate tumor and normal prostate, and to be expressed at lower levels in all other tissues tested. 1D-4279 was found to be over-expressed in prostate tumor and normal prostate, expressed at lower levels in normal spinal cord, and to be undetectable in all other tissues
5 tested.

Further microarray analysis to specifically address the extent to which P501S (SEQ ID NO: 110) was expressed in breast tumor revealed moderate over-expression not only in breast tumor, but also in metastatic breast tumor (2/31), with negligible to low expression in normal tissues. This data suggests that P501S may be over-
10 expressed in various breast tumors as well as in prostate tumors.

The expression levels of 32 ESTs (expressed sequence tags) described by Vasmatazis *et al.* (*Proc. Natl. Acad. Sci. USA* 95:300-304, 1998) in a variety of tumor and normal tissues were examined by microarray technology as described above. Two of these clones (referred to as P1000C and P1001C) were found to be over-expressed in prostate
15 tumor and normal prostate, and expressed at low to undetectable levels in all other tissues tested (normal aorta, thymus, resting and activated PBMC, epithelial cells, spinal cord, adrenal gland, fetal tissues, skin, salivary gland, large intestine, bone marrow, liver, lung, dendritic cells, stomach, lymph nodes, brain, heart, small intestine, skeletal muscle, colon and kidney. The determined cDNA sequences for P1000C and P1001C are provided in
20 SEQ ID NO: 384 and 472, respectively. The sequence of P1001C was found to show some homology to the previously isolated Human mRNA for JM27 protein. No significant homologies were found to the sequence of P1000C.

The expression of the polypeptide encoded by the full length cDNA sequence for F1-12 (also referred to as P504S; SEQ ID NO: 108) was investigated by
25 immunohistochemical analysis. Rabbit-anti-P504S polyclonal antibodies were generated against the full length P504S protein by standard techniques. Subsequent isolation and characterization of the polyclonal antibodies were also performed by techniques well known in the art. Immunohistochemical analysis showed that the P504S polypeptide was expressed in 100% of prostate carcinoma samples tested (n=5).

The rabbit-anti-P504S polyclonal antibody did not appear to label benign prostate cells with the same cytoplasmic granular staining, but rather with light nuclear staining. Analysis of normal tissues revealed that the encoded polypeptide was found to be expressed in some, but not all normal human tissues. Positive cytoplasmic staining with
 5 rabbit-anti-P504S polyclonal antibody was found in normal human kidney, liver, brain, colon and lung-associated macrophages, whereas heart and bone marrow were negative.

This data indicates that the P504S polypeptide is present in prostate cancer tissues, and that there are qualitative and quantitative differences in the staining between benign prostatic hyperplasia tissues and prostate cancer tissues, suggesting that this
 10 polypeptide may be detected selectively in prostate tumors and therefore be useful in the diagnosis of prostate cancer.

EXAMPLE 3

ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC 15 POLYPEPTIDES BY PCR-BASED SUBTRACTION

A cDNA subtraction library, containing cDNA from normal prostate subtracted with ten other normal tissue cDNAs (brain, heart, kidney, liver, lung, ovary, placenta, skeletal muscle, spleen and thymus) and then submitted to a first round of PCR
 20 amplification, was purchased from Clontech. This library was subjected to a second round of PCR amplification, following the manufacturer's protocol. The resulting cDNA fragments were subcloned into the vector pT7 Blue T-vector (Novagen, Madison, WI) and transformed into XL-1 Blue MRF' *E. coli* (Stratagene). DNA was isolated from independent clones and sequenced using a Perkin Elmer/Applied Biosystems Division
 25 Automated Sequencer Model 373A.

Fifty-nine positive clones were sequenced. Comparison of the DNA sequences of these clones with those in the gene bank, as described above, revealed no significant homologies to 25 of these clones, hereinafter referred to as P5, P8, P9, P18, P20, P30, P34, P36, P38, P39, P42, P49, P50, P53, P55, P60, P64, P65, P73, P75, P76, P79

and P84. The determined cDNA sequences for these clones are provided in SEQ ID NO: 41-45, 47-52 and 54-65, respectively. P29, P47, P68, P80 and P82 (SEQ ID NO: 46, 53 and 66-68, respectively) were found to show some degree of homology to previously identified DNA sequences. To the best of the inventors' knowledge, none of these sequences have been previously shown to be present in prostate.

Further studies employing the sequence of SEQ ID NO: 67 as a probe in standard full-length cloning methods, resulted in the isolation of three cDNA sequences which appear to be splice variants of P80 (also known as P704P). These sequences are provided in SEQ ID NO: 699-701.

Further studies using the PCR-based methodology described above resulted in the isolation of more than 180 additional clones, of which 23 clones were found to show no significant homologies to known sequences. The determined cDNA sequences for these clones are provided in SEQ ID NO: 115-123, 127, 131, 137, 145, 147-151, 153, 156-158 and 160. Twenty-three clones (SEQ ID NO: 124-126, 128-130, 132-136, 138-144, 146, 152, 154, 155 and 159) were found to show some homology to previously identified ESTs. An additional ten clones (SEQ ID NO: 161-170) were found to have some degree of homology to known genes. Larger cDNA clones containing the P20 sequence represent splice variants of a gene referred to as P703P. The determined DNA sequence for the variants referred to as DE1, DE13 and DE14 are provided in SEQ ID NOS: 171, 175 and 177, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 172, 176 and 178, respectively. The determined cDNA sequence for an extended spliced form of P703 is provided in SEQ ID NO: 225. The DNA sequences for the splice variants referred to as DE2 and DE6 are provided in SEQ ID NOS: 173 and 174, respectively.

mRNA Expression levels for representative clones in tumor tissues (prostate (n=5), breast (n=2), colon and lung) normal tissues (prostate (n=5), colon, kidney, liver, lung (n=2), ovary (n=2), skeletal muscle, skin, stomach, small intestine and brain), and activated and non-activated PBMC was determined by RT-PCR as described above. Expression was examined in one sample of each tissue type unless otherwise indicated.

P9 was found to be highly expressed in normal prostate and prostate tumor compared to all normal tissues tested except for normal colon which showed comparable expression. P20, a portion of the P703P gene, was found to be highly expressed in normal prostate and prostate tumor, compared to all twelve normal tissues tested. A modest increase in expression of P20 in breast tumor (n=2), colon tumor and lung tumor was seen compared to all normal tissues except lung (1 of 2). Increased expression of P18 was found in normal prostate, prostate tumor and breast tumor compared to other normal tissues except lung and stomach. A modest increase in expression of P5 was observed in normal prostate compared to most other normal tissues. However, some elevated expression was seen in normal lung and PBMC. Elevated expression of P5 was also observed in prostate tumors (2 of 5), breast tumor and one lung tumor sample. For P30, similar expression levels were seen in normal prostate and prostate tumor, compared to six of twelve other normal tissues tested. Increased expression was seen in breast tumors, one lung tumor sample and one colon tumor sample, and also in normal PBMC. P29 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to the majority of normal tissues. However, substantial expression of P29 was observed in normal colon and normal lung (2 of 2). P80 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to all other normal tissues tested, with increased expression also being seen in colon tumor.

Further studies resulted in the isolation of twelve additional clones, hereinafter referred to as 10-d8, 10-h10, 11-c8, 7-g6, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3, 8-h11, 9-f12 and 9-f3. The determined DNA sequences for 10-d8, 10-h10, 11-c8, 8-d4, 8-d9, 8-h11, 9-f12 and 9-f3 are provided in SEQ ID NO: 207, 208, 209, 216, 217, 220, 221 and 222, respectively. The determined forward and reverse DNA sequences for 7-g6, 8-b5, 8-b6 and 8-g3 are provided in SEQ ID NO: 210 and 211; 212 and 213; 214 and 215; and 218 and 219, respectively. Comparison of these sequences with those in the gene bank revealed no significant homologies to the sequence of 9-f3. The clones 10-d8, 11-c8 and 8-h11 were found to show some homology to previously isolated ESTs, while 10-h10, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3 and 9-f12 were found to show some homology to previously identified genes.

Further characterization of 7-G6 and 8-G3 showed identity to the known genes PAP and PSA, respectively.

mRNA expression levels for these clones were determined using the micro-array technology described above. The clones 7-G6, 8-G3, 8-B5, 8-B6, 8-D4, 8-D9, 9-F3, 9-F12, 9-H3, 10-A2, 10-A4, 11-C9 and 11-F2 were found to be over-expressed in prostate tumor and normal prostate, with expression in other tissues tested being low or undetectable. Increased expression of 8-F11 was seen in prostate tumor and normal prostate, bladder, skeletal muscle and colon. Increased expression of 10-H10 was seen in prostate tumor and normal prostate, bladder, lung, colon, brain and large intestine. Increased expression of 9-B1 was seen in prostate tumor, breast tumor, and normal prostate, salivary gland, large intestine and skin, with increased expression of 11-C8 being seen in prostate tumor, and normal prostate and large intestine.

An additional cDNA fragment derived from the PCR-based normal prostate subtraction, described above, was found to be prostate specific by both micro-array technology and RT-PCR. The determined cDNA sequence of this clone (referred to as 9-A11) is provided in SEQ ID NO: 226. Comparison of this sequence with those in the public databases revealed 99% identity to the known gene HOXB13.

Further studies led to the isolation of the clones 8-C6 and 8-H7. The determined cDNA sequences for these clones are provided in SEQ ID NO: 227 and 228, respectively. These sequences were found to show some homology to previously isolated ESTs.

PCR and hybridization-based methodologies were employed to obtain longer cDNA sequences for clone P20 (also referred to as P703P), yielding three additional cDNA fragments that progressively extend the 5' end of the gene. These fragments, referred to as P703PDE5, P703P6.26, and P703PX-23 (SEQ ID NO: 326, 328 and 330, with the predicted corresponding amino acid sequences being provided in SEQ ID NO: 327, 329 and 331, respectively) contain additional 5' sequence. P703PDE5 was recovered by screening of a cDNA library (#141-26) with a portion of P703P as a probe. P703P6.26 was recovered from a mixture of three prostate tumor cDNAs and P703PX_23 was

recovered from cDNA library (#438-48). Together, the additional sequences include all of the putative mature serine protease along with part of the putative signal sequence. The full-length cDNA sequence for P703P is provided in SEQ ID NO: 524, with the corresponding amino acid sequence being provided in SEQ ID NO: 525.

5 P703P was found to show some homology to previously identified proteases, such as thrombin. The thrombin receptor has been shown to be preferentially expressed in highly metastatic breast carcinoma cells and breast carcinoma biopsy samples. Introduction of thrombin receptor antisense cDNA has been shown to inhibit the invasion of metastatic breast carcinoma cells in culture. Antibodies against thrombin receptor
10 inhibit thrombin receptor activation and thrombin-induced platelet activation. Furthermore, peptides that resemble the receptor's tethered ligand domain inhibit platelet aggregation by thrombin. P703P may play a role in prostate cancer through a protease-activated receptor on the cancer cell or on stromal cells. The potential trypsin-like protease activity of P703P may either activate a protease-activated receptor on the cancer cell
15 membrane to promote tumorigenesis or activate a protease-activated receptor on the adjacent cells (such as stromal cells) to secrete growth factors and/or proteases (such as matrix metalloproteinases) that could promote tumor angiogenesis, invasion and metastasis. P703P may thus promote tumor progression and/or metastasis through the activation of protease-activated receptor. Polypeptides and antibodies that block the
20 P703P-receptor interaction may therefore be usefully employed in the treatment of prostate cancer.

Further studies using a PCR-based subtraction library of a prostate tumor pool subtracted against a pool of normal tissues (referred to as JP: PCR subtraction) resulted in the isolation of thirteen additional clones, seven of which did not share any
25 significant homology to known GenBank sequences. The determined cDNA sequences for these seven clones (P711P, P712P, novel 23, P774P, P775P, P710P and P768P) are provided in SEQ ID NO: 307-311, 313 and 315, respectively. The remaining six clones (SEQ ID NO: 316 and 321-325) were shown to share some homology to known genes. By microarray analysis, all thirteen clones showed three or more fold over-expression in

prostate tissues, including prostate tumors, BPH and normal prostate as compared to normal non-prostate tissues. Clones P711P, P712P, novel 23 and P768P showed over-expression in most prostate tumors and BPH tissues tested (n=29), and in the majority of normal prostate tissues (n=4), but background to low expression levels in all normal
5 tissues. Clones P774P, P775P and P710P showed comparatively lower expression and expression in fewer prostate tumors and BPH samples, with negative to low expression in normal prostate.

Further studies led to the isolation of an extended cDNA sequence for P712P (SEQ ID NO: 552). The amino acid sequences encoded by 16 predicted open
10 reading frames present within the sequence of SEQ ID NO: 552 are provided in SEQ ID NO: 553-568.

The full-length cDNA for P711P was obtained by employing the partial sequence of SEQ ID NO: 307 to screen a prostate cDNA library. Specifically, a directionally cloned prostate cDNA library was prepared using standard techniques. One
15 million colonies of this library were plated onto LB/Amp plates. Nylon membrane filters were used to lift these colonies, and the cDNAs which were picked up by these filters were denatured and cross-linked to the filters by UV light. The P711P cDNA fragment of SEQ ID NO: 307 was radio-labeled and used to hybridize with these filters. Positive clones were selected, and cDNAs were prepared and sequenced using an automatic Perkin
20 Elmer/Applied Biosystems sequencer. The determined full-length sequence of P711P is provided in SEQ ID NO: 382, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 383.

Using PCR and hybridization-based methodologies, additional cDNA sequence information was derived for two clones described above, 11-C9 and 9-F3, herein
25 after referred to as P707P and P714P, respectively (SEQ ID NO: 333 and 334). After comparison with the most recent GenBank, P707P was found to be a splice variant of the known gene HoxB13. In contrast, no significant homologies to P714P were found. Further studies employing the sequence of SEQ ID NO: 334 as a probe in standard full-length cloning methods, resulted in an extended cDNA sequence for P714P. This sequence

is provided in SEQ ID NO: 698. This sequence was found to show some homology to the gene that encodes human ribosomal L23A protein.

Clones 8-B3, P89, P98, P130 and P201 (as disclosed in U.S. Patent Application No. 09/020,956, filed February 9, 1998) were found to be contained within one
 5 contiguous sequence, referred to as P705P (SEQ ID NO: 335, with the predicted amino acid sequence provided in SEQ ID NO: 336), which was determined to be a splice variant of the known gene NKX 3.1.

Further studies on P775P resulted in the isolation of four additional sequences (SEQ ID NO: 473-476) which are all splice variants of the P775P gene. The
 10 sequence of SEQ ID NO: 474 was found to contain two open reading frames (ORFs). The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 477 and 478. The cDNA sequence of SEQ ID NO: 475 was found to contain an ORF which encodes the amino acid sequence of SEQ ID NO: 479. The cDNA sequence of SEQ ID NO: 473 was found to contain four ORFs. The predicted amino acid sequences encoded by
 15 these ORFs are provided in SEQ ID NO: 480-483. Additional splice variants of P775P are provided in SEQ ID NO: 593-597.

Subsequent studies led to the identification of a genomic region on chromosome 22q11.2, known as the Cat Eye Syndrome region, that contains the five prostate genes P704P, P712P, P774P, P775P and B305D. The relative location of each of
 20 these five genes within the genomic region is shown in Fig. 10. This region may therefore be associated with malignant tumors, and other potential tumor genes may be contained within this region. These studies also led to the identification of a potential open reading frame (ORF) for P775P (provided in SEQ ID NO: 533), which encodes the amino acid sequence of SEQ ID NO: 534.

25 Comparison of the clone of SEQ ID NO: 325 (referred to as P558S) with sequences in the GenBank and GeneSeq DNA databases showed that P558S is identical to the prostate-specific transglutaminase gene, which is known to have two forms. The full-length sequences for the two forms are provided in SEQ ID NO: 773 and 774, with the corresponding amino acid sequences being provided in SEQ ID NO: 775 and 776,

respectively. The cDNA sequence of SEQ ID NO: 774 has a 15 pair base insert, resulting in a 5 amino acid insert in the corresponding amino acid sequence (SEQ ID NO: 776). This insert is not present in the sequence of SEQ ID NO: 773.

5

EXAMPLE 4

SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

20

EXAMPLE 5

FURTHER ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC POLYPEPTIDES BY PCR-BASED SUBTRACTION

25

A cDNA library generated from prostate primary tumor mRNA as described above was subtracted with cDNA from normal prostate. The subtraction was performed using a PCR-based protocol (Clontech), which was modified to generate larger fragments. Within this protocol, tester and driver double stranded cDNA were separately digested with

five restriction enzymes that recognize six-nucleotide restriction sites (MluI, MscI, PvuII, SalI and StuI). This digestion resulted in an average cDNA size of 600 bp, rather than the average size of 300 bp that results from digestion with RsaI according to the Clontech protocol. This modification did not affect the subtraction efficiency. Two tester
5 populations were then created with different adapters, and the driver library remained without adapters.

The tester and driver libraries were then hybridized using excess driver cDNA. In the first hybridization step, driver was separately hybridized with each of the two tester cDNA populations. This resulted in populations of (a) unhybridized tester
10 cDNAs, (b) tester cDNAs hybridized to other tester cDNAs, (c) tester cDNAs hybridized to driver cDNAs and (d) unhybridized driver cDNAs. The two separate hybridization reactions were then combined, and rehybridized in the presence of additional denatured driver cDNA. Following this second hybridization, in addition to populations (a) through (d), a fifth population (e) was generated in which tester cDNA with one adapter hybridized
15 to tester cDNA with the second adapter. Accordingly, the second hybridization step resulted in enrichment of differentially expressed sequences which could be used as templates for PCR amplification with adaptor-specific primers.

The ends were then filled in, and PCR amplification was performed using adaptor-specific primers. Only population (e), which contained tester cDNA that did not
20 hybridize to driver cDNA, was amplified exponentially. A second PCR amplification step was then performed, to reduce background and further enrich differentially expressed sequences.

This PCR-based subtraction technique normalizes differentially expressed cDNAs so that rare transcripts that are overexpressed in prostate tumor tissue may be
25 recoverable. Such transcripts would be difficult to recover by traditional subtraction methods.

In addition to genes known to be overexpressed in prostate tumor, seventy-seven further clones were identified. Sequences of these partial cDNAs are provided in SEQ ID NO: 29 to 305. Most of these clones had no significant homology to database

sequences. Exceptions were JTPN23 (SEQ ID NO: 231; similarity to pig valosin-containing protein), JTPN30 (SEQ ID NO: 234; similarity to rat mRNA for proteasome subunit), JTPN45 (SEQ ID NO: 243; similarity to rat *norvegicus* cytosolic NADP-dependent isocitrate dehydrogenase), JTPN46 (SEQ ID NO: 244; similarity to human subclone H8 4 d4 DNA sequence), JP1D6 (SEQ ID NO: 265; similarity to *G. gallus* dynein light chain-A), JP8D6 (SEQ ID NO: 288; similarity to human BAC clone RG016J04), JP8F5 (SEQ ID NO: 289; similarity to human subclone H8 3 b5 DNA sequence), and JP8E9 (SEQ ID NO: 299; similarity to human Alu sequence).

Additional studies using the PCR-based subtraction library consisting of a prostate tumor pool subtracted against a normal prostate pool (referred to as PT-PN PCR subtraction) yielded three additional clones. Comparison of the cDNA sequences of these clones with the most recent release of GenBank revealed no significant homologies to the two clones referred to as P715P and P767P (SEQ ID NO: 312 and 314). The remaining clone was found to show some homology to the known gene KIAA0056 (SEQ ID NO: 318). Using microarray analysis to measure mRNA expression levels in various tissues, all three clones were found to be over-expressed in prostate tumors and BPH tissues. Specifically, clone P715P was over-expressed in most prostate tumors and BPH tissues by a factor of three or greater, with elevated expression seen in the majority of normal prostate samples and in fetal tissue, but negative to low expression in all other normal tissues. Clone P767P was over-expressed in several prostate tumors and BPH tissues, with moderate expression levels in half of the normal prostate samples, and background to low expression in all other normal tissues tested.

Further analysis, by microarray as described above, of the PT-PN PCR subtraction library and of a DNA subtraction library containing cDNA from prostate tumor subtracted with a pool of normal tissue cDNAs, led to the isolation of 27 additional clones (SEQ ID NO: 340-365 and 381) which were determined to be over-expressed in prostate tumor. The clones of SEQ ID NO: 341, 342, 345, 347, 348, 349, 351, 355-359, 361, 362 and 364 were also found to be expressed in normal prostate. Expression of all 26 clones in a variety of normal tissues was found to be low or undetectable, with the exception of

P544S (SEQ ID NO: 356) which was found to be expressed in small intestine. Of the 26 clones, 11 (SEQ ID NO: 340-349 and 362) were found to show some homology to previously identified sequences. No significant homologies were found to the clones of SEQ ID NO: 350, 351, 353-361, and 363-365.

5 Comparison of the sequence of SEQ ID NO: 362 with sequences in the GenBank and GeneSeq DNA databases showed that this clone (referred to as P788P) is identical to GeneSeq Accession No. X27262, which encodes a protein found in the GeneSeq protein Accession No. Y00931. The full length cDNA sequence of P788P is shown in Figure 12A (SEQ ID NO: 777), with the corresponding predicted amino acid
10 being shown in Figure 12B (SEQ ID NO: 778). Subsequently, a full-length cDNA sequence for P788P that contains polymorphisms not found in the sequence of SEQ ID NO: 779, was cloned multiple times by PCR amplification from cDNA prepared from several RNA templates from three individuals. This determined cDNA sequence of this polymorphic variant of P788P is provided in SEQ ID NO: 779, with the corresponding
15 amino acid sequence being provided in SEQ ID NO: 780. The sequence of SEQ ID NO: 780 differs from that of SEQ ID NO: 778 by six amino acid residues. The P788P protein has 7 potential transmembrane domains at the C-terminal portion and is predicted to be a plasma membrane protein with an extracellular N-terminal region.

 Further studies on the clone of SEQ ID NO: 352 (referred to as P790P) led
20 to the isolation of the full-length cDNA sequence of SEQ ID NO: 526. The corresponding predicted amino acid is provided in SEQ ID NO: 527. Data from two quantitative PCR experiments indicated that P790P is over-expressed in 11/15 tested prostate tumor samples and is expressed at low levels in spinal cord, with no expression being seen in all other normal samples tested. Data from further PCR experiments and microarray experiments
25 showed over-expression in normal prostate and prostate tumor with little or no expression in other tissues tested. P790P was subsequently found to show significant homology to a previously identified G-protein coupled prostate tissue receptor.

 Additional studies on the clone of SEQ ID NO: 354 (referred to as P776P) led to the isolation of an extended cDNA sequence, provided in SEQ ID NO: 569. The

determined cDNA sequences of three additional splice variants of P776P are provided in SEQ ID NO: 570-572. The amino acid sequences encoded by two predicted open reading frames (ORFs) contained within SEQ ID NO: 570, one predicted ORF contained within SEQ ID NO: 571, and 11 predicted ORFs contained within SEQ ID NO: 569, are provided
 5 in SEQ ID NO: 573-586, respectively.

Comparison of the cDNA sequences for the clones P767P (SEQ ID NO: 314) and P777P (SEQ ID NO: 350) with sequences in the GenBank human EST database showed that the two clones matched many EST sequences in common, suggesting that P767P and P777P may represent the same gene. A DNA consensus sequence derived
 10 from a DNA sequence alignment of P767P, P777P and multiple EST clones is provided in SEQ ID NO: 587. The amino acid sequences encoded by three putative ORFs located within SEQ ID NO: 587 are provided in SEQ ID NO: 588-590.

EXAMPLE 6

15 PEPTIDE PRIMING OF MICE AND PROPAGATION OF CTL LINES

6.1. This Example illustrates the preparation of a CTL cell line specific for cells expressing the P502S gene.

Mice expressing the transgene for human HLA A2Kb (provided by Dr L.
 20 Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with P2S#12 peptide (VLGWVAEL; SEQ ID NO: 306), which is derived from the P502S gene (also referred to herein as J1-17, SEQ ID NO: 8), as described by Theobald et al., *Proc. Natl. Acad. Sci. USA* 92:11993-11997, 1995 with the following modifications. Mice were immunized with 100µg of P2S#12 and 120µg of an I-A^b binding peptide derived from
 25 hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and using a nylon mesh single cell suspensions prepared. Cells were then resuspended at 6×10^6 cells/ml in complete media (RPMI-1640; Gibco BRL, Gaithersburg, MD) containing 10% FCS, 2mM Glutamine (Gibco BRL), sodium pyruvate (Gibco BRL), non-essential amino acids (Gibco BRL), 2×10^{-5} M 2-mercaptoethanol,

50U/ml penicillin and streptomycin, and cultured in the presence of irradiated (3000 rads) P2S#12-pulsed (5mg/ml P2S#12 and 10mg/ml β 2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7 μ g/ml dextran sulfate and 25 μ g/ml LPS for 3 days). Six days later, cells (5×10^5 /ml) were restimulated with 2.5×10^6 /ml peptide pulsed irradiated (20,000 rads) EL4A2Kb cells (Sherman et al, *Science* 258:815-818, 1992) and 3×10^6 /ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20U/ml IL-2. Cells continued to be restimulated on a weekly basis as described, in preparation for cloning the line.

P2S#12 line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells (1×10^4 cells/ well) as stimulators and A2 transgenic spleen cells as feeders (5×10^5 cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, clones that were growing were isolated and maintained in culture. Several of these clones demonstrated significantly higher reactivity (lysis) against human fibroblasts (HLA A2Kb expressing) transduced with P502S than against control fibroblasts. An example is presented in Figure 1.

This data indicates that P2S #12 represents a naturally processed epitope of the P502S protein that is expressed in the context of the human HLA A2Kb molecule.

6.2. This Example illustrates the preparation of murine CTL lines and CTL clones specific for cells expressing the P501S gene.

This series of experiments were performed similarly to that described above. Mice were immunized with the P1S#10 peptide (SEQ ID NO: 337), which is derived from the P501S gene (also referred to herein as L1-12, SEQ ID NO: 110). The P1S#10 peptide was derived by analysis of the predicted polypeptide sequence for P501S for potential HLA-A2 binding sequences as defined by published HLA-A2 binding motifs (Parker, KC, et al, *J. Immunol.*, 152:163, 1994). P1S#10 peptide was synthesized as described in Example 4, and empirically tested for HLA-A2 binding using a T cell based competition assay. Predicted A2 binding peptides were tested for their ability to compete HLA-A2 specific peptide presentation to an HLA-A2 restricted CTL clone (D150M58), which is

specific for the HLA-A2 binding influenza matrix peptide fluM58. D150M58 CTL secretes TNF in response to self-presentation of peptide fluM58. In the competition assay, test peptides at 100-200 $\mu\text{g/ml}$ were added to cultures of D150M58 CTL in order to bind HLA-A2 on the CTL. After thirty minutes, CTL cultured with test peptides, or control peptides, were tested for their antigen dose response to the fluM58 peptide in a standard TNF bioassay. As shown in Figure 3, peptide P1S#10 competes HLA-A2 restricted presentation of fluM58, demonstrating that peptide P1S#10 binds HLA-A2.

Mice expressing the transgene for human HLA A2Kb were immunized as described by Theobald et al. (*Proc. Natl. Acad. Sci. USA* 92:11993-11997, 1995) with the following modifications. Mice were immunized with 62.5 μg of P1S #10 and 120 μg of an I-A^b binding peptide derived from Hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and single cell suspensions prepared using a nylon mesh. Cells were then resuspended at 6×10^6 cells/ml in complete media (as described above) and cultured in the presence of irradiated (3000 rads) P1S#10-pulsed (2 $\mu\text{g/ml}$ P1S#10 and 10mg/ml β 2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7 $\mu\text{g/ml}$ dextran sulfate and 25 $\mu\text{g/ml}$ LPS for 3 days). Six days later cells (5×10^5 /ml) were restimulated with 2.5×10^6 /ml peptide-pulsed irradiated (20,000 rads) EL4A2Kb cells, as described above, and 3×10^6 /ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20 U/ml IL-2. Cells were restimulated on a weekly basis in preparation for cloning. After three rounds of *in vitro* stimulations, one line was generated that recognized P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat targets as shown in Figure 4.

A P1S#10-specific CTL line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells (1×10^4 cells/ well) as stimulators and A2 transgenic spleen cells as feeders (5×10^5 cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, viable clones were isolated and maintained in culture. As shown in Figure 5, five of these clones demonstrated specific cytolytic reactivity against P501S-transduced Jurkat A2Kb targets. This data indicates that

P1S#10 represents a naturally processed epitope of the P501S protein that is expressed in the context of the human HLA-A2.1 molecule.

EXAMPLE 7

5 PRIMING OF CTL *IN VIVO* USING NAKED DNA IMMUNIZATION WITH A PROSTATE ANTIGEN

The prostate-specific antigen L1-12, as described above, is also referred to as P501S. HLA A2Kb Tg mice (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with 100 µg P501S in the vector VR1012 either
10 intramuscularly or intradermally. The mice were immunized three times, with a two week interval between immunizations. Two weeks after the last immunization, immune spleen cells were cultured with Jurkat A2Kb-P501S transduced stimulator cells. CTL lines were stimulated weekly. After two weeks of *in vitro* stimulation, CTL activity was assessed against P501S transduced targets. Two out of 8 mice developed strong anti-P501S CTL
15 responses. These results demonstrate that P501S contains at least one naturally processed HLA-A2-restricted CTL epitope.

EXAMPLE 8

20 ABILITY OF HUMAN T CELLS TO RECOGNIZE PROSTATE-SPECIFIC POLYPEPTIDES

This Example illustrates the ability of T cells specific for a prostate tumor polypeptide to recognize human tumor.

Human CD8⁺ T cells were primed *in vitro* to the P2S-12 peptide (SEQ ID NO: 306) derived from P502S (also referred to as J1-17) using dendritic cells according to
25 the protocol of Van Tsai et al. (*Critical Reviews in Immunology* 18:65-75, 1998). The resulting CD8⁺ T cell microcultures were tested for their ability to recognize the P2S-12 peptide presented by autologous fibroblasts or fibroblasts which were transduced to express the P502S gene in a γ -interferon ELISPOT assay (see Lalvani et al., *J. Exp. Med.* 186:859-865, 1997). Briefly, titrating numbers of T cells were assayed in duplicate on 10⁴

fibroblasts in the presence of 3 $\mu\text{g/ml}$ human β_2 -microglobulin and 1 $\mu\text{g/ml}$ P2S-12 peptide or control E75 peptide. In addition, T cells were simultaneously assayed on autologous fibroblasts transduced with the P502S gene or as a control, fibroblasts transduced with HER-2/*neu*. Prior to the assay, the fibroblasts were treated with 10 ng/ml γ -interferon for 5 48 hours to upregulate class I MHC expression. One of the microcultures (#5) demonstrated strong recognition of both peptide pulsed fibroblasts as well as transduced fibroblasts in a γ -interferon ELISPOT assay. Figure 2A demonstrates that there was a strong increase in the number of γ -interferon spots with increasing numbers of T cells on fibroblasts pulsed with the P2S-12 peptide (solid bars) but not with the control E75 peptide 10 (open bars). This shows the ability of these T cells to specifically recognize the P2S-12 peptide. As shown in Figure 2B, this microculture also demonstrated an increase in the number of γ -interferon spots with increasing numbers of T cells on fibroblasts transduced to express the P502S gene but not the HER-2/*neu* gene. These results provide additional confirmatory evidence that the P2S-12 peptide is a naturally processed epitope of the 15 P502S protein. Furthermore, this also demonstrates that there exists in the human T cell repertoire, high affinity T cells which are capable of recognizing this epitope. These T cells should also be capable of recognizing human tumors which express the P502S gene.

EXAMPLE 9

20 ELICITATION OF PROSTATE ANTIGEN-SPECIFIC CTL RESPONSES IN HUMAN BLOOD

This Example illustrates the ability of a prostate-specific antigen to elicit a CTL response in blood of normal humans.

25 Autologous dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal donors by growth for five days in RPMI medium containing 10% human serum, 50 ng/ml GMCSF and 30 ng/ml IL-4. Following culture, DC were infected overnight with recombinant P501S-expressing vaccinia virus at an M.O.I. of 5 and matured for 8 hours by the addition of 2 micrograms/ml CD40 ligand. Virus was

inactivated by UV irradiation, CD8⁺ cells were isolated by positive selection using magnetic beads, and priming cultures were initiated in 24-well plates. Following five stimulation cycles using autologous fibroblasts retrovirally transduced to express P501S and CD80, CD8⁺ lines were identified that specifically produced interferon-gamma when stimulated with autologous P501S-transduced fibroblasts. The P501S-specific activity of cell line 3A-1 could be maintained following additional stimulation cycles on autologous B-LCL transduced with P501S. Line 3A-1 was shown to specifically recognize autologous B-LCL transduced to express P501S, but not EGFP-transduced autologous B-LCL, as measured by cytotoxicity assays (⁵¹Cr release) and interferon-gamma production (Interferon-gamma Elispot; *see above and Lalvani et al., J. Exp. Med.* 186:859-865, 1997). The results of these assays are presented in Figures 6A and 6B.

EXAMPLE 10

IDENTIFICATION OF A NATURALLY PROCESSED CTL EPIOTOPE CONTAINED WITHIN A PROSTATE-SPECIFIC ANTIGEN

The 9-mer peptide p5 (SEQ ID NO: 338) was derived from the P703P antigen (also referred to as P20). The p5 peptide is immunogenic in human HLA-A2 donors and is a naturally processed epitope. Antigen specific human CD8⁺ T cells can be primed following repeated *in vitro* stimulations with monocytes pulsed with p5 peptide. These CTL specifically recognize p5-pulsed and P703P-transduced target cells in both ELISPOT (as described above) and chromium release assays. Additionally, immunization of HLA-A2Kb transgenic mice with p5 leads to the generation of CTL lines which recognize a variety of HLA-A2Kb or HLA-A2 transduced target cells expressing P703P.

Initial studies demonstrating that p5 is a naturally processed epitope were done using HLA-A2Kb transgenic mice. HLA-A2Kb transgenic mice were immunized subcutaneously in the footpad with 100 µg of p5 peptide together with 140 µg of hepatitis B virus core peptide (a Th peptide) in Freund's incomplete adjuvant. Three weeks post immunization, spleen cells from immunized mice were stimulated *in vitro* with peptide-

pulsed LPS blasts. CTL activity was assessed by chromium release assay five days after primary *in vitro* stimulation. Retrovirally transduced cells expressing the control antigen P703P and HLA-A2Kb were used as targets. CTL lines that specifically recognized both p5-pulsed targets as well as P703P-expressing targets were identified.

5 Human *in vitro* priming experiments demonstrated that the p5 peptide is immunogenic in humans. Dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by culturing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, the DC were pulsed with 1 ug/ml p5 peptide and cultured with CD8+ T
10 cell enriched PBMC. CTL lines were restimulated on a weekly basis with p5-pulsed monocytes. Five to six weeks after initiation of the CTL cultures, CTL recognition of p5-pulsed target cells was demonstrated. CTL were additionally shown to recognize human cells transduced to express P703P, demonstrating that p5 is a naturally processed epitope.

Studies identifying a further peptide epitope (referred to as peptide 4)
15 derived from the prostate tumor-specific antigen P703P that is capable of being recognized by CD4 T cells on the surface of cells in the context of HLA class II molecules were carried out as follows. The amino acid sequence for peptide 4 is provided in SEQ ID NO: 781, with the corresponding cDNA sequence being provided in SEQ ID NO: 782.

Twenty 15-mer peptides overlapping by 10 amino acids and derived from
20 the carboxy-terminal fragment of P703P were generated using standard procedures. Dendritic cells (DC) were derived from PBMC of a normal female donor using GM-CSF and IL-4 by standard protocols. CD4 T cells were generated from the same donor as the DC using MACS beads and negative selection. DC were pulsed overnight with pools of the 15-mer peptides, with each peptide at a final concentration of 0.25 microgram/ml.
25 Pulsed DC were washed and plated at 1×10^4 cells/well of 96-well V-bottom plates and purified CD4 T cells were added at 1×10^5 /well. Cultures were supplemented with 60 ng/ml IL-6 and 10 ng/ml IL-12 and incubated at 37 °C. Cultures were restimulated as above on a weekly basis using DC generated and pulsed as above as antigen presenting cells, supplemented with 5 ng/ml IL-7 and 10 u/ml IL-2. Following 4 *in vitro* stimulation
30 cycles, 96 lines (each line corresponding to one well) were tested for specific proliferation

and cytokine production in response to the stimulating pools with an irrelevant pool of peptides derived from mammaglobin being used as a control.

One line (referred to as 1-F9) was identified from pool #1 that demonstrated specific proliferation (measured by 3H proliferation assays) and cytokine production (measured by interferon-gamma ELISA assays) in response to pool #1 of P703P peptides. This line was further tested for specific recognition of the peptide pool, specific recognition of individual peptides in the pool, and in HLA mismatch analyses to identify the relevant restricting allele. Line 1-F9 was found to specifically proliferate and produce interferon-gamma in response to peptide pool #1, and also to peptide 4 (SEQ ID NO: 781). Peptide 4 corresponds to amino acids 126-140 of SEQ ID NO: 327. Peptide titration experiments were conducted to assess the sensitivity of line 1-F9 for the specific peptide. The line was found to specifically respond to peptide 4 at concentrations as low as 0.25 ng/ml, indicating that the T cells are very sensitive and therefore likely to have high affinity for the epitope.

To determine the HLA restriction of the P703P response, a panel of antigen presenting cells (APC) was generated that was partially matched with the donor used to generate the T cells. The APC were pulsed with the peptide and used in proliferation and cytokine assays together with line 1-F9. APC matched with the donor at HLA-DRB0701 and HLA-DQB02 alleles were able to present the peptide to the T cells, indicating that the P703P-specific response is restricted to one of these alleles.

Antibody blocking assays were utilized to determine if the restricting allele was HLA-DR0701 or HLA-DQ02. The anti-HLA-DR blocking antibody L243 or an irrelevant isotype matched IgG2a were added to T cells and APC cultures pulsed with the peptide RMPTVLQCVNVS VVS (SEQ ID NO: 781) at 250 ng/ml. Standard interferon-gamma and proliferation assays were performed. Whereas the control antibody had no effect on the ability of the T cells to recognize peptide-pulsed APC, in both assays the anti-HLA-DR antibody completely blocked the ability of the T cells to specifically recognize peptide-pulsed APC.

To determine if the peptide epitope RMPTVLQCVNVS VVS (SEQ ID NO: 781) was naturally processed, the ability of line 1-F9 to recognize APC pulsed with recombinant P703P protein was examined. For these experiments a number of recombinant

P703P sources were utilized; E. coli-derived P703P, Pichia-derived P703P and baculovirus-derived P703P. Irrelevant protein controls used were E. coli derived-L3E and baculovirus-derived mammaglobin. In interferon-gamma ELISA assays, line 1-F9 was able to efficiently recognize both E. coli forms of P703P as well as Pichia-derived
 5 recombinant P703P, while baculovirus-derived P703P was recognized less efficiently. Subsequent Western blot analysis revealed that the E coli and Pichia P703P protein preparations were intact while the baculovirus P703P preparation was approximately 75% degraded. Thus, peptide RMPTVLQCVNVSVVS (SEQ ID NO: 781) from P703P is a naturally processed peptide epitope derived from P703P and presented to T cells in the
 10 context of HLA-DRB-0701

In further studies, twenty-four 15-mer peptides overlapping by 10 amino acids and derived from the N-terminal fragment of P703P (corresponding to amino acids 27-154 of SEQ ID NO: 525) were generated by standard procedures and their ability to be recognized by CD4 cells was determined essentially as described above. DC were pulsed
 15 overnight with pools of the peptides with each peptide at a final concentration of 10 microgram/ml. A large number of individual CD4 T cell lines (65/480) demonstrated significant proliferation and cytokine release (IFN-gamma) in response to the P703P peptide pools but not to a control peptide pool. The CD4 T cell lines which demonstrated specific activity were restimulated on the appropriate pool of P703P peptides and reassayed
 20 on the individual peptides of each pool as well as a peptide dose titration of the pool of peptides in a IFN-gamma release assay and in a proliferation assay.

Sixteen immunogenic peptides were recognized by the T cells from the entire set of peptide antigens tested. The amino acid sequences of these peptides are provided in SEQ ID NO: 799-814, with the corresponding cDNA sequences being
 25 provided in SEQ ID NO: 783-798, respectively. In some cases the peptide reactivity of the T cell line could be mapped to a single peptide, however some could be mapped to more than one peptide in each pool. Those CD4 T cell lines that displayed a representative pattern of recognition from each peptide pool with a reasonable affinity for peptide were chosen for further analysis (I-1A, -6A; II-4C, -5E; III-6E, IV-4B, -3F, -9B, -10F, V-5B, -
 30 4D, and -10F). These CD4 T cells lines were restimulated on the appropriate individual

peptide and reassayed on autologous DC pulsed with a truncated form of recombinant P703P protein made in *E. coli* (a.a. 96 - 254 of SEQ ID NO: 525), full-length P703P made in the baculovirus expression system, and a fusion between influenza virus NS1 and P703P made in *E. coli*. Of the T cell lines tested, line I-1A recognized specifically the truncated
5 form of P703P (*E. coli*) but no other recombinant form of P703P. This line also recognized the peptide used to elicit the T cells. Line 2-4C recognized the truncated form of P703P (*E. coli*) and the full length form of P703P made in baculovirus, as well as peptide. The remaining T cell lines tested were either peptide-specific only (II-5E, II-6F, IV-4B, IV-3F, IV-9B, IV-10F, V-5B and V-4D) or were non-responsive to any antigen tested (V-10F).
10 These results demonstrate that the peptide sequence RPLLANDLMLIKLDE (SEQ ID NO: 814; corresponding to a.a. 110-124 of SEQ ID NO: 525) recognized by the T cell line I-1A, and the peptide sequences SVSESDTIRSISIAS (SEQ ID NO: 811; corresponding to a.a. 125-139 of SEQ ID NO: 525) and ISIASQCPTAGNSCL (SEQ ID NO: 810; corresponding to a.a. 135-149 of SEQ ID NO: 525) recognized by the T cell line II-4C may be naturally
15 processed epitopes of the P703P protein.

EXAMPLE 11

EXPRESSION OF A BREAST TUMOR-DERIVED ANTIGEN IN PROSTATE

20

Isolation of the antigen B305D from breast tumor by differential display is described in US Patent Application No. 08/700,014, filed August 20, 1996. Several different splice forms of this antigen were isolated. The determined cDNA sequences for these splice forms are provided in SEQ ID NO: 366-375, with the predicted amino acid
25 sequences corresponding to the sequences of SEQ ID NO: 292, 298 and 301-303 being provided in SEQ ID NO: 299-306, respectively. In further studies, a splice variant of the cDNA sequence of SEQ ID NO: 366 was isolated which was found to contain an additional guanine residue at position 884 (SEQ ID NO: 530), leading to a frameshift in the open reading frame. The determined DNA sequence of this ORF is provided in SEQ ID NO:

531. This frameshift generates a protein sequence (provided in SEQ ID NO: 532) of 293 amino acids that contains the C-terminal domain common to the other isoforms of B305D but that differs in the N-terminal region.

The expression levels of B305D in a variety of tumor and normal tissues were examined by real time PCR and by Northern analysis. The results indicated that B305D is highly expressed in breast tumor, prostate tumor, normal prostate and normal testes, with expression being low or undetectable in all other tissues examined (colon tumor, lung tumor, ovary tumor, and normal bone marrow, colon, kidney, liver, lung, ovary, skin, small intestine, stomach). Using real-time PCR on a panel of prostate tumors, expression of B305D in prostate tumors was shown to increase with increasing Gleason grade, demonstrating that expression of B305D increases as prostate cancer progresses.

EXAMPLE 12

GENERATION OF HUMAN CTL *IN VITRO* USING WHOLE GENE PRIMING AND STIMULATION

TECHNIQUES WITH PROSTATE-SPECIFIC ANTIGEN

Using *in vitro* whole-gene priming with P501S-vaccinia infected DC (see, for example, Yee et al, *The Journal of Immunology*, 157(9):4079-86, 1996), human CTL lines were derived that specifically recognize autologous fibroblasts transduced with P501S (also known as L1-12), as determined by interferon- γ ELISPOT analysis as described above. Using a panel of HLA-mismatched B-LCL lines transduced with P501S, these CTL lines were shown to be likely restricted to HLAB class I allele. Specifically, dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by growing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, DC were infected overnight with recombinant P501S vaccinia virus at a multiplicity of infection (M.O.I) of five, and matured overnight by the addition of 3 μ g/ml CD40 ligand. Virus was inactivated by UV irradiation. CD8⁺ T cells were isolated using a magnetic bead system, and priming cultures were initiated using standard culture techniques. Cultures were restimulated every

7-10 days using autologous primary fibroblasts retrovirally transduced with P501S and CD80. Following four stimulation cycles, CD8⁺ T cell lines were identified that specifically produced interferon- γ when stimulated with P501S and CD80-transduced autologous fibroblasts. A panel of HLA-mismatched B-LCL lines transduced with P501S
 5 were generated to define the restriction allele of the response. By measuring interferon- γ in an ELISPOT assay, the P501S specific response was shown to be likely restricted by HLA B alleles. These results demonstrate that a CD8⁺ CTL response to P501S can be elicited.

To identify the epitope(s) recognized, cDNA encoding P501S was fragmented by various restriction digests, and sub-cloned into the retroviral expression
 10 vector pBIB-KS. Retroviral supernatants were generated by transfection of the helper packaging line Phoenix-Ampho. Supernatants were then used to transduce Jurkat/A2Kb cells for CTL screening. CTL were screened in IFN- γ ELISPOT assays against these A2Kb targets transduced with the “library” of P501S fragments. Initial positive fragments P501S/H3 and P501S/F2 were sequenced and found to encode amino acids 106-553 and
 15 amino acids 136-547, respectively, of SEQ ID NO: 113. A truncation of H3 was made to encode amino acid residues 106-351 of SEQ ID NO: 113, which was unable to stimulate the CTL, thus localizing the epitope to amino acid residues 351-547. Additional fragments encoding amino acids 1-472 (Fragment A) and amino acids 1-351 (Fragment B) were also constructed. Fragment A but not Fragment B stimulated the CTL thus localizing the
 20 epitope to amino acid residues 351-472. Overlapping 20-mer and 18-mer peptides representing this region were tested by pulsing Jurkat/A2Kb cells versus CTL in an IFN- γ assay. Only peptides P501S-369(20) and P501S-369(18) stimulated the CTL. Nine-mer and 10-mer peptides representing this region were synthesized and similarly tested. Peptide P501S-370 (SEQ ID NO: 539) was the minimal 9-mer giving a strong
 25 response. Peptide P501S-376 (SEQ ID NO: 540) also gave a weak response, suggesting that it might represent a cross-reactive epitope.

In subsequent studies, the ability of primary human B cells transduced with P501S to prime MHC class I-restricted, P501S-specific, autologous CD8 T cells was examined. Primary B cells were derived from PBMC of a homozygous HLA-A2 donor by

culture in CD40 ligand and IL-4, transduced at high frequency with recombinant P501S in the vector pBIB, and selected with blastocidin-S. For *in vitro* priming, purified CD8+ T cells were cultured with autologous CD40 ligand + IL-4 derived, P501S-transduced B cells in a 96-well microculture format. These CTL microcultures were re-stimulated with

5 P501S-transduced B cells and then assayed for specificity. Following this initial screen, microcultures with significant signal above background were cloned on autologous EBV-transformed B cells (BLCL), also transduced with P501S. Using IFN-gamma ELISPOT for detection, several of these CD8 T cell clones were found to be specific for P501S, as demonstrated by reactivity to BLCL/P501S but not BLCL transduced with control antigen.

10 It was further demonstrated that the anti-P501S CD8 T cell specificity is HLA-A2-restricted. First, antibody blocking experiments with anti-HLA-A,B,C monoclonal antibody (W6.32), anti-HLA-B,C monoclonal antibody (B1.23.2) and a control monoclonal antibody showed that only the anti-HLA-A,B,C antibody blocked recognition of P501S-expressing autologous BLCL. Secondly, the anti-P501S CTL also recognized an HLA-A2

15 matched, heterologous BLCL transduced with P501S, but not the corresponding EGFP transduced control BLCL.

EXAMPLE 13

IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS

20 BY MICROARRAY ANALYSIS

This Example describes the isolation of certain prostate-specific polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library as described above was

25 screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate normal tissues (not including testis). 372 clones were identified, and 319 were successfully sequenced. Table I presents a summary of these clones, which are shown in SEQ ID NOs:385-400. Of these sequences SEQ ID NOs:386, 389, 390 and 392 correspond to

novel genes, and SEQ ID NOs: 393 and 396 correspond to previously identified sequences. The others (SEQ ID NOs:385, 387, 388, 391, 394, 395 and 397-400) correspond to known sequences, as shown in Table I.

Table I

002690-037990

Summary of Prostate Tumor Antigens

Known Genes	Previously Identified Genes	Novel Genes
T-cell gamma chain	P504S	23379 (SEQ ID NO:389)
Kallikrein	P1000C	23399 (SEQ ID NO:392)
Vector	P501S	23320 (SEQ ID NO:386)
CGI-82 protein mRNA (23319; SEQ ID NO:385)	P503S	23381 (SEQ ID NO:390)
PSA	P510S	
Ald. 6 Dehyd.	P784P	
L-idoitol-2 dehydrogenase (23376; SEQ ID NO:388)	P502S	
Ets transcription factor PDEF (22672; SEQ ID NO:398)	P706P	
hTGR (22678; SEQ ID NO:399)	19142.2, bangur.seq (22621; SEQ ID NO:396)	
KIAA0295(22685; SEQ ID NO:400)	5566.1 Wang (23404; SEQ ID NO:393)	
Prostatic Acid Phosphatase(22655; SEQ ID NO:397)	P712P	
transglutaminase (22611; SEQ ID NO:395)	P778P	
HDLBP (23508; SEQ ID NO:394)		
CGI-69 Protein(23367; SEQ ID NO:387)		
KIAA0122(23383; SEQ ID NO:391)		
TEEG		

CGI-82 showed 4.06 fold over-expression in prostate tissues as compared to
5 other normal tissues tested. It was over-expressed in 43% of prostate tumors, 25% normal

prostate, not detected in other normal tissues tested. L-iditol-2 dehydrogenase showed 4.94 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 90% of prostate tumors, 100% of normal prostate, and not detected in other normal tissues tested. Ets transcription factor PDEF showed 5.55 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% prostate tumors, 25% normal prostate and not detected in other normal tissues tested. hTGR1 showed 9.11 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 63% of prostate tumors and is not detected in normal tissues tested including normal prostate. KIAA0295 showed 5.59 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% of prostate tumors, low to undetectable in normal tissues tested including normal prostate tissues. Prostatic acid phosphatase showed 9.14 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 67% of prostate tumors, 50% of normal prostate, and not detected in other normal tissues tested. Transglutaminase showed 14.84 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 30% of prostate tumors, 50% of normal prostate, and is not detected in other normal tissues tested. High density lipoprotein binding protein (HDLBP) showed 28.06 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% of normal prostate, and is undetectable in all other normal tissues tested. CGI-69 showed 3.56 fold over-expression in prostate tissues as compared to other normal tissues tested. It is a low abundant gene, detected in more than 90% of prostate tumors, and in 75% normal prostate tissues. The expression of this gene in normal tissues was very low. KIAA0122 showed 4.24 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 57% of prostate tumors, it was undetectable in all normal tissues tested including normal prostate tissues. 19142.2 bangur showed 23.25 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors and 100% of normal prostate. It was undetectable in other normal tissues tested. 5566.1 Wang showed 3.31 fold over-

expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% normal prostate and was also over-expressed in normal bone marrow, pancreas, and activated PBMC. Novel clone 23379 (also referred to as P553S) showed 4.86 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in 97% of prostate tumors and 75% normal prostate and is undetectable in all other normal tissues tested. Novel clone 23399 showed 4.09 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 27% of prostate tumors and was undetectable in all normal tissues tested including normal prostate tissues. Novel clone 23320 showed 3.15 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in all prostate tumors and 50% of normal prostate tissues. It was also expressed in normal colon and trachea. Other normal tissues do not express this gene at high level.

Subsequent full-length cloning studies on P553S, using standard techniques, revealed that this clone is an incomplete spliced form of P501S. The determined cDNA sequences for four splice variants of P553S are provided in SEQ ID NO: 702-705. An amino acid sequence encoded by SEQ ID NO: 705 is provided in SEQ ID NO: 706. The cDNA sequence of SEQ ID NO: 702 was found to contain two open reading frames (ORFs). The amino acid sequences encoded by these two ORFs are provided in SEQ ID NO: 707 and 708.

EXAMPLE 14

IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS

BY ELECTRONIC SUBTRACTION

This Example describes the use of an electronic subtraction technique to identify prostate-specific antigens.

Potential prostate-specific genes present in the GenBank human EST database were identified by electronic subtraction (similar to that described by Vasmatizis et al., *Proc. Natl. Acad. Sci. USA* 95:300-304, 1998). The sequences of EST clones

(43,482) derived from various prostate libraries were obtained from the GenBank public human EST database. Each prostate EST sequence was used as a query sequence in a BLASTN (National Center for Biotechnology Information) search against the human EST database. All matches considered identical (length of matching sequence >100 base pairs, density of identical matches over this region > 70%) were grouped (aligned) together in a cluster. Clusters containing more than 200 ESTs were discarded since they probably represented repetitive elements or highly expressed genes such as those for ribosomal proteins. If two or more clusters shared common ESTs, those clusters were grouped together into a “supercluster,” resulting in 4,345 prostate superclusters.

Records for the 479 human cDNA libraries represented in the GenBank release were downloaded to create a database of these cDNA library records. These 479 cDNA libraries were grouped into three groups: Plus (normal prostate and prostate tumor libraries, and breast cell line libraries, in which expression was desired), Minus (libraries from other normal adult tissues, in which expression was not desirable), and Other (libraries from fetal tissue, infant tissue, tissues found only in women, non-prostate tumors and cell lines other than prostate cell lines, in which expression was considered to be irrelevant). A summary of these library groups is presented in Table II.

Table II

Prostate cDNA Libraries and ESTs

Library	# of Libraries	# of ESTs
Plus	25	43,482
Normal	11	18,875
Tumor	11	21,769
Cell lines	3	2,838
Minus	166	
Other	287	

Each supercluster was analyzed in terms of the ESTs within the supercluster. The tissue source of each EST clone was noted and used to classify the superclusters into four groups: Type 1- EST clones found in the Plus group libraries only; no expression detected in Minus or Other group libraries; Type 2- EST clones derived from the Plus and Other group libraries only; no expression detected in the Minus group; Type 3- EST clones derived from the Plus, Minus and Other group libraries, but the number of ESTs derived from the Plus group is higher than in either the Minus or Other groups; and Type 4- EST clones derived from Plus, Minus and Other group libraries, but the number derived from the Plus group is higher than the number derived from the Minus group. This analysis identified 4,345 breast clusters (*see* Table III). From these clusters, 3,172 EST clones were ordered from Research Genetics, Inc., and were received as frozen glycerol stocks in 96-well plates.

Table III
Prostate Cluster Summary

Type	# of Superclusters	# of ESTs Ordered
1	688	677
2	2899	2484
3	85	11
4	673	0
Total	4345	3172

The EST clone inserts were PCR-amplified using amino-linked PCR primers for Synteni microarray analysis. When more than one PCR product was obtained for a particular clone, that PCR product was not used for expression analysis. In total, 2,528 clones from the electronic subtraction method were analyzed by microarray analysis to identify electronic subtraction breast clones that had high levels of tumor vs. normal

tissue mRNA. Such screens were performed using a Synteni (Palo Alto, CA) microarray, according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA* 93:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA* 94:2150-2155, 1997). Within these analyses, the clones were arrayed on the chip, which was then probed with fluorescent probes generated from normal and tumor prostate cDNA, as well as various other normal tissues. The slides were scanned and the fluorescence intensity was measured.

Clones with an expression ratio greater than 3 (*i.e.*, the level in prostate tumor and normal prostate mRNA was at least three times the level in other normal tissue mRNA) were identified as prostate tumor-specific sequences (Table IV). The sequences of these clones are provided in SEQ ID NO: 401-453, with certain novel sequences shown in SEQ ID NO: 407, 413, 416-419, 422, 426, 427 and 450.

Table IV

Prostate-tumor Specific Clones

SEQ ID NO.	Sequence Designation	Comments
401	22545	previously identified P1000C
402	22547	previously identified P704P
403	22548	known
404	22550	known
405	22551	PSA
406	22552	prostate secretory protein 94
407	22553	novel
408	22558	previously identified P509S
409	22562	glandular kallikrein
410	22565	previously identified P1000C
411	22567	PAP
412	22568	B1006C (breast tumor antigen)
413	22570	novel
414	22571	PSA
415	22572	previously identified P706P
416	22573	novel
417	22574	novel

418	22575	novel
419	22580	novel
420	22581	PAP
421	22582	prostatic secretory protein 94
422	22583	novel
423	22584	prostatic secretory protein 94
424	22585	prostatic secretory protein 94
425	22586	known
426	22587	novel
427	22588	novel
428	22589	PAP
429	22590	known
430	22591	PSA
431	22592	known
432	22593	Previously identified P777P
433	22594	T cell receptor gamma chain
434	22595	Previously identified P705P
435	22596	Previously identified P707P
436	22847	PAP
437	22848	known
438	22849	prostatic secretory protein 57
439	22851	PAP
440	22852	PAP
441	22853	PAP
442	22854	previously identified P509S
443	22855	previously identified P705P
444	22856	previously identified P774P
445	22857	PSA
446	23601	previously identified P777P
447	23602	PSA
448	23605	PSA
449	23606	PSA
450	23612	novel
451	23614	PSA
452	23618	previously identified P1000C
453	23622	previously identified P705P

Further studies on the clone of SEQ ID NO: 407 (also referred to as P1020C) led to the isolation of an extended cDNA sequence provided in SEQ ID NO: 591. This extended cDNA sequence was found to contain an open reading frame that encodes

the predicted amino acid sequence of SEQ ID NO: 592. The P1020C cDNA and amino acid sequences were found to show some similarity to the human endogenous retroviral HERV-K pol gene and protein.

5

EXAMPLE 15

FURTHER IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS BY MICROARRAY ANALYSIS

This Example describes the isolation of additional prostate-specific polypeptides from a prostate tumor cDNA library.

10

A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate normal tissues (not including testis). 142 clones were identified and sequenced. Certain of these clones are shown in SEQ ID NO: 454-467. Of these sequences, SEQ ID NO: 459-15 461 represent novel genes. The others (SEQ ID NO: 454-458 and 461-467) correspond to known sequences.

EXAMPLE 16

FURTHER CHARACTERIZATION OF PROSTATE-SPECIFIC ANTIGEN P710P

20

This Example describes the full length cloning of P710P.

The prostate cDNA library described above was screened with the P710P fragment described above. One million colonies were plated on LB/Ampicillin plates. Nylon membrane filters were used to lift these colonies, and the cDNAs picked up by these 25 filters were then denatured and cross-linked to the filters by UV light. The P710P fragment was radiolabeled and used to hybridize with the filters. Positive cDNA clones were selected and their cDNAs recovered and sequenced by an automatic Perkin Elmer/Applied Biosystems Division Sequencer. Four sequences were obtained, and are presented in SEQ ID NO: 468-471. These sequences appear to represent different splice variants of the

P710P gene. Subsequent comparison of the cDNA sequences of P710P with those in Genbank revealed homology to the DD3 gene (Genbank accession numbers AF103907 & AF103908). The cDNA sequence of DD3 is provided in SEQ ID NO: 690.

5

EXAMPLE 17

PROTEIN EXPRESSION OF PROSTATE-SPECIFIC ANTIGENS

This example describes the expression and purification of prostate-specific antigens in *E. coli*, baculovirus and mammalian cells.

10 **A) EXPRESSION OF P501S IN *E. COLI***

Expression of the full-length form of P501S was attempted by first cloning P501S without the leader sequence (amino acids 36-553 of SEQ ID NO: 113) downstream of the first 30 amino acids of the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 484) in pET17b. Specifically, P501S DNA was used to perform PCR using the primers AW025 (SEQ ID NO: 485) and AW003 (SEQ ID NO: 486). AW025 is a sense cloning primer that contains a HindIII site. AW003 is an antisense cloning primer that contains an EcoRI site. DNA amplification was performed using 5 µl 10X Pfu buffer, 1 µl 20 mM dNTPs, 1 µl each of the PCR primers at 10 µM concentration, 40 µl water, 1 µl Pfu DNA polymerase (Stratagene, La Jolla, CA) and 1 µl DNA at 100 ng/µl. Denaturation at 95°C was performed for 30 sec, followed by 10 cycles of 95°C for 30 sec, 60°C for 1 min and by 72°C for 3 min. 20 cycles of 95°C for 30 sec, 65°C for 1 min and by 72°C for 3 min, and lastly by 1 cycle of 72°C for 10 min. The PCR product was cloned to Ra12m/pET17b using HindIII and EcoRI. The sequence of the resulting fusion construct (referred to as Ra12-P501S-F) was confirmed by DNA sequencing.

25 The fusion construct was transformed into BL21(DE3)pLysE, pLysS and CodonPlus *E. coli* (Stratagene) and grown overnight in LB broth with kanamycin. The resulting culture was induced with IPTG. Protein was transferred to PVDF membrane and blocked with 5% non-fat milk (in PBS-Tween buffer), washed three times and incubated

with mouse anti-His tag antibody (Clontech) for 1 hour. The membrane was washed 3 times and probed with HRP-Protein A (Zymed) for 30 min. Finally, the membrane was washed 3 times and developed with ECL (Amersham). No expression was detected by Western blot. Similarly, no expression was detected by Western blot when the Ra12-P501S-F fusion was used for expression in BL21CodonPlus by CE6 phage (Invitrogen).

An N-terminal fragment of P501S (amino acids 36-325 of SEQ ID NO: 113) was cloned down-stream of the first 30 amino acids of the *M. tuberculosis* antigen Ra12 in pET17b as follows. P501S DNA was used to perform PCR using the primers AW025 (SEQ ID NO: 485) and AW027 (SEQ ID NO: 487). AW027 is an antisense cloning primer that contains an EcoRI site and a stop codon. DNA amplification was performed essentially as described above. The resulting PCR product was cloned to Ra12 in pET17b at the HindIII and EcoRI sites. The fusion construct (referred to as Ra12-P501S-N) was confirmed by DNA sequencing.

The Ra12-P501S-N fusion construct was used for expression in BL21(DE3)pLysE, pLysS and CodonPlus, essentially as described above. Using Western blot analysis, protein bands were observed at the expected molecular weight of 36 kDa. Some high molecular weight bands were also observed, probably due to aggregation of the recombinant protein. No expression was detected by Western blot when the Ra12-P501S-F fusion was used for expression in BL21CodonPlus by CE6 phage.

A fusion construct comprising a C-terminal portion of P501S (amino acids 257-553 of SEQ ID NO: 113) located down-stream of the first 30 amino acids of the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 484) was prepared as follows. P501S DNA was used to perform PCR using the primers AW026 (SEQ ID NO: 488) and AW003 (SEQ ID NO: 486). AW026 is a sense cloning primer that contains a HindIII site. DNA amplification was performed essentially as described above. The resulting PCR product was cloned to Ra12 in pET17b at the HindIII and EcoRI sites. The sequence for the fusion construct (referred to as Ra12-P501S-C) was confirmed.

The Ra12-P501S-C fusion construct was used for expression in BL21(DE3)pLysE, pLysS and CodonPlus, as described above. A small amount of protein

was detected by Western blot, with some molecular weight aggregates also being observed. Expression was also detected by Western blot when the Ra12-P501S-C fusion was used for expression in BL21CodonPlus induced by CE6 phage.

B) EXPRESSION OF P501S IN BACULOVIRUS

5 The Bac-to-Bac baculovirus expression system (BRL Life Technologies, Inc.) was used to express P501S protein in insect cells. Full-length P501S (SEQ ID NO: 113) was amplified by PCR and cloned into the XbaI site of the donor plasmid pFastBacI. The recombinant bacmid and baculovirus were prepared according to the manufacturer's instructions. The recombinant baculovirus was amplified in Sf9 cells and the high titer viral stocks were utilized to infect High Five cells (Invitrogen) to make the recombinant protein. The identity of the full-length protein was confirmed by N-terminal sequencing of the recombinant protein and by Western blot analysis (Figure 7). Specifically, 0.6 million High Five cells in 6-well plates were infected with either the unrelated control virus BV/ECD_PD (lane 2), with recombinant baculovirus for P501S at different amounts or MOIs (lanes 4-8), or were uninfected (lane 3). Cell lysates were run on SDS-PAGE under reducing conditions and analyzed by Western blot with the anti-P501S monoclonal antibody P501S-10E3-G4D3 (prepared as described below). Lane 1 is the biotinylated protein molecular weight marker (BioLabs).

20 The localization of recombinant P501S in the insect cells was investigated as follows. The insect cells overexpressing P501S were fractionated into fractions of nucleus, mitochondria, membrane and cytosol. Equal amounts of protein from each fraction were analyzed by Western blot with a monoclonal antibody against P501S. Due to the scheme of fractionation, both nucleus and mitochondria fractions contain some plasma membrane components. However, the membrane fraction is basically free from mitochondria and nucleus. P501S was found to be present in all fractions that contain the membrane component, suggesting that P501S may be associated with plasma membrane of the insect cells expressing the recombinant protein.

C) EXPRESSION OF P501S IN MAMMALIAN CELLS

Full-length P501S (553AA) was cloned into various mammalian expression vectors, including pCEP4 (Invitrogen), pVR1012 (Vical, San Diego, CA) and a modified form of the retroviral vector pBMN, referred to as pBIB. Transfection of P501S/pCEP4 and P501S/pVR1012 into HEK293 fibroblasts was carried out using the Fugene transfection reagent (Boehringer Mannheim). Briefly, 2 μ l of Fugene reagent was diluted into 100 μ l of serum-free media and incubated at room temperature for 5-10 min. This mixture was added to 1 μ g of P501S plasmid DNA, mixed briefly and incubated for 30 minutes at room temperature. The Fugene/DNA mixture was added to cells and incubated for 24-48 hours. Expression of recombinant P501S in transfected HEK293 fibroblasts was detected by means of Western blot employing a monoclonal antibody to P501S.

Transfection of p501S/pCEP4 into CHO-K cells (American Type Culture Collection, Rockville, MD) was carried out using GenePorter transfection reagent (Gene Therapy Systems, San Diego, CA). Briefly, 15 μ l of GenePorter was diluted in 500 μ l of serum-free media and incubated at room temperature for 10 min. The GenePorter/media mixture was added to 2 μ g of plasmid DNA that was diluted in 500 μ l of serum-free media, mixed briefly and incubated for 30 min at room temperature. CHO-K cells were rinsed in PBS to remove serum proteins, and the GenePorter/DNA mix was added and incubated for 5 hours. The transfected cells were then fed an equal volume of 2x media and incubated for 24-48 hours.

FACS analysis of P501S transiently infected CHO-K cells, demonstrated surface expression of P501S. Expression was detected using rabbit polyclonal antisera raised against a P501S peptide, as described below. Flow cytometric analysis was performed using a FaCScan (Becton Dickinson), and the data were analyzed using the Cell Quest program.

D) EXPRESSION OF P703P IN BACULOVIRUS

The cDNA for full-length P703P-DE5 (SEQ ID NO: 326), together with several flanking restriction sites, was obtained by digesting the plasmid pCDNA703 with

restriction endonucleases Xba I and Hind III. The resulting restriction fragment (approx. 800 base pairs) was ligated into the transfer plasmid pFastBacI which was digested with the same restriction enzymes. The sequence of the insert was confirmed by DNA sequencing. The recombinant transfer plasmid pFBP703 was used to make recombinant bacmid DNA and baculovirus using the Bac-To-Bac Baculovirus expression system (BRL Life Technologies). High Five cells were infected with the recombinant virus BVP703, as described above, to obtain recombinant P703P protein.

E) EXPRESSION OF P788P IN *E. COLI*

A truncated, N-terminal portion, of P788P (residues 1-644 of SEQ ID NO: 777; referred to as P788P-N) fused with a C-terminal 6xHis Tag was expressed in *E. coli* as follows. P788P cDNA was amplified using the primers AW080 and AW081 (SEQ ID NO: 815 and 816). AW080 is a sense cloning primer with an NdeI site. AW081 is an antisense cloning primer with a XhoI site. The PCR-amplified P788P, as well as the vector pCRX1, were digested with NdeI and XhoI. Vector and insert were ligated and transformed into NovaBlue cells. Colonies were randomly screened for insert and then sequenced. P788P-N clone #6 was confirmed to be identical to the designed construct. The expression construct P788P-N #6/pCRX1 was transformed into *E. coli* BL21 CodonPlus-RIL competent cells. After induction, most of the cells grew well, achieving OD600 of greater than 2.0 after 3 hr. Coomassie stained SDS-PAGE showed an over-expressed band at about 75 kD. Western blot analysis using a 6xHisTag antibody confirmed the band was P788P-N. The determined cDNA sequence for P788P-N is provided in SEQ ID NO: 817, with the corresponding amino acid sequence being provided in SEQ ID NO: 818.

F) EXPRESSION OF P510S IN *E. COLI*

The P510S protein has 9 potential transmembrane domains and is predicted to be located at the plasma membrane. The C-terminal protein of this protein, as well as the predicted third extracellular domain of P510S were expressed in *E. coli* as follows.

The expression construct referred to as Ra12-P501S-C was designed to have a 6 HisTag at the N-terminal end, followed by the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 819) and then the C-terminal portion of P510S (amino residues 1176-1261 of SEQ ID NO: 538). Full-length P510S was used to amplify the P510S-C fragment by PCR using the primers AW056 and AW057 (SEQ ID NO: 820 and 821, respectively). AW056 is a sense cloning primer with an EcoRI site. AW057 is an antisense primer with stop and XhoI sites. The amplified P501S fragment and Ra12/pCRX1 were digested with EcoRI and XhoI and then purified. The insert and vector were ligated together and transformed into NovaBlue. Colonies were randomly screened for insert and sequences. For protein expression, the expression construct was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL competent cells. A mini-induction screen was performed to optimize the expression conditions. After induction the cells grew well, achieving OD 600 nm greater than 2.0 after 3 hours. Coomassie stain SDS-PAGE showed a highly over-expressed band at approx. 30 kD. Though this is higher than the expected molecular weight, western blot analysis was positive, showing this band to be the His tag-containing protein. The optimized culture conditions are as follows. Dilute overnight culture/daytime culture (LB + kanamycin + chloramphenicol) into 2xYT (with kanamycin and chloramphenicol) at a ratio of 25 ml culture to 1 liter 2xYT. Allow to grow at 37 °C until OD600 = 0.6. Take an aliquot out as T0 sample. Add 1 mM IPTG and allow to grow at 30 °C for 3 hours. Take out a T3 sample, spin down cells and store at -80 °C. The determined cDNA and amino acid sequences for the Ra12-P510S-C construct are provided in SEQ ID NO: 822 and 825, respectively.

The expression construct P510S-C was designed to have a 5' added start codon and a glycine (GGA) codon and then the P510S C terminal fragment followed by the in frame 6x histidine tag and stop codon from the pET28b vector. The cloning strategy is similar to that used for Ra12-P510S-C, except that the PCR primers employed were those shown in SEQ ID NO: 828 and 829, respectively and the NcoI/XhoI cut in pET28b was used. The primer of SEQ ID NO: 828 created a 5' NcoI site and added a start codon. The antisense primer of SEQ ID NO: 829 creates a XhoI site on P510S C terminal fragment. Clones

were confirmed by sequencing. For protein expression, the expression construct was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL competent cells. An OD600 of greater than 2.0 was obtained 30 hours after induction. Coomassie stained SDS-PAGE showed an over-expressed band at about 11 kD. Western blot analysis confirmed that the

5 band was P510S-C, as did N-terminal protein sequencing. The optimized culture conditions are as follows: dilute overnight culture/daytime culture (LB + kanamycin + chloramphenicol) into 2x YT (+ kanamycin and chloramphenicol) at a ratio of 25 mL culture to 1 liter 2x YT, and allow to grow at 37 °C until an OD 600 of about 0.5 is reached. Take out an aliquot as T0 sample. Add 1 mM IPTG and allow to grow at 30 °C

10 for 3 hours. Spin down the cells and store at -80 °C until purification. The determined cDNA and amino acid sequence for the P510S-C construct are shown in SEQ ID NO: 823 and 826, respectively.

The predicted third extracellular domain of P510S (P510S-E3; residues 328-676 of SEQ ID NO: 538) was expressed in *E. coli* as follows. The P510S fragment was

15 amplified by PCR using the primers shown in SEQ ID NO: 830 and 831. The primer of SEQ ID NO: 830 is a sense primer with an NdeI site for use in ligating into pPDM. The primer of SEQ ID NO: 831 is an antisense primer with an added XhoI site for use in ligating into pPDM. The resulting fragment was cloned to pPDM at the NdeI and XhoI sites. Clones were confirmed by sequencing. For protein expression, the clone was

20 transformed into *E. coli* BL21 (DE3) CodonPlus-RIL competent cells. After induction, an OD600 of greater than 2.0 was achieved after 3 hours. Coomassie stained SDS-PAGE showed an over-expressed band at about 39 kD, and N-terminal sequencing confirmed the N-terminal to be that of P510S-E3. Optimized culture conditions are as follows: dilute overnight culture/daytime culture (LB + kanamycin + chloramphenicol) into 2x YT

25 (kanamycin and chloramphenicol) at a ratio of 25 ml culture to 1 liter 2x YT. Allow to grow at 37 °C until OD 600 equals 0.6. Take out an aliquot as T0 sample. Add 1 mM IPTG and allow to grow at 30 °C for 3 hours. Take out a T3 sample, spin down the cells and store at -80 °C until purification. The determined cDNA and amino acid sequences for the P510S-E3 construct are provided in SEQ ID NO: 824 and 827, respectively.

G) EXPRESSION OF P775S IN *E. COLI*

The antigen P775P contains multiple open reading frames (ORF). The third ORF, encoding the protein of SEQ ID NO: 483, has the best emotif score. An expression fusion construct containing the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 819) and P775P-ORF3 with an N-terminal 6x HisTag was prepared as follows. P775P-ORF3 was amplified using the sense PCR primers of SEQ ID NO: 832 and the anti-sense PCR primer of SEQ ID NO: 833. The PCR amplified fragment of P775P and Ra12/pCRX1 were digested with the restriction enzymes EcoRI and XhoI. Vector and insert were ligated and then transformed into NovaBlue cells. Colonies were randomly screened for insert and then sequenced. A clone having the desired sequence was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL competent cells. Two hours after induction, the cell density peaked at OD600 of approximately 1.8. Coomassie stained SDS-PAGE showed an over-expressed band at about 31 kD. Western blot using 6x HisTag antibody confirmed that the band was Ra12-P775P-ORF3. The determined cDNA and amino acid sequences for the fusion construct are provided in SEQ ID NO: 834 and 835, respectively.

EXAMPLE 18

PREPARATION AND CHARACTERIZATION OF ANTIBODIES

AGAINST PROSTATE-SPECIFIC POLYPEPTIDES

A) PREPARATION AND CHARACTERIZATION OF POLYCLONAL ANTIBODIES AGAINST P703P, P504S AND P509S

Polyclonal antibodies against P703P, P504S and P509S were prepared as follows.

Each prostate tumor antigen expressed in an *E. coli* recombinant expression system was grown overnight in LB broth with the appropriate antibiotics at 37°C in a shaking incubator. The next morning, 10 ml of the overnight culture was added to 500 ml

to 2x YT plus appropriate antibiotics in a 2L-baffled Erlenmeyer flask. When the Optical Density (at 560 nm) of the culture reached 0.4-0.6, the cells were induced with IPTG (1 mM). Four hours after induction with IPTG, the cells were harvested by centrifugation. The cells were then washed with phosphate buffered saline and centrifuged again. The supernatant was discarded and the cells were either frozen for future use or immediately processed. Twenty ml of lysis buffer was added to the cell pellets and vortexed. To break open the *E. coli* cells, this mixture was then run through the French Press at a pressure of 16,000 psi. The cells were then centrifuged again and the supernatant and pellet were checked by SDS-PAGE for the partitioning of the recombinant protein. For proteins that localized to the cell pellet, the pellet was resuspended in 10 mM Tris pH 8.0, 1% CHAPS and the inclusion body pellet was washed and centrifuged again. This procedure was repeated twice more. The washed inclusion body pellet was solubilized with either 8 M urea or 6 M guanidine HCl containing 10 mM Tris pH 8.0 plus 10 mM imidazole. The solubilized protein was added to 5 ml of nickel-chelate resin (Qiagen) and incubated for 45 min to 1 hour at room temperature with continuous agitation. After incubation, the resin and protein mixture were poured through a disposable column and the flow through was collected. The column was then washed with 10-20 column volumes of the solubilization buffer. The antigen was then eluted from the column using 8M urea, 10 mM Tris pH 8.0 and 300 mM imidazole and collected in 3 ml fractions. A SDS-PAGE gel was run to determine which fractions to pool for further purification.

As a final purification step, a strong anion exchange resin such as HiPrepQ (Biorad) was equilibrated with the appropriate buffer and the pooled fractions from above were loaded onto the column. Each antigen was eluted off the column with a increasing salt gradient. Fractions were collected as the column was run and another SDS-PAGE gel was run to determine which fractions from the column to pool. The pooled fractions were dialyzed against 10 mM Tris pH 8.0. The proteins were then vialled after filtration through a 0.22 micron filter and the antigens were frozen until needed for immunization.

Four hundred micrograms of each prostate antigen was combined with 100 micrograms of muramyl dipeptide (MDP). Every four weeks rabbits were boosted with 100

micrograms mixed with an equal volume of Incomplete Freund's Adjuvant (IFA). Seven days following each boost, the animal was bled. Sera was generated by incubating the blood at 4°C for 12-4 hours followed by centrifugation.

Ninety-six well plates were coated with antigen by incubating with 50 microliters (typically 1 microgram) of recombinant protein at 4 °C for 20 hours. 250 microliters of BSA blocking buffer was added to the wells and incubated at room temperature for 2 hours. Plates were washed 6 times with PBS/0.01% Tween. Rabbit sera was diluted in PBS. Fifty microliters of diluted sera was added to each well and incubated at room temperature for 30 min. Plates were washed as described above before 50 microliters of goat anti-rabbit horse radish peroxidase (HRP) at a 1:10000 dilution was added and incubated at room temperature for 30 min. Plates were again washed as described above and 100 microliters of TMB microwell peroxidase substrate was added to each well. Following a 15 min incubation in the dark at room temperature, the colorimetric reaction was stopped with 100 microliters of 1N H₂SO₄ and read immediately at 450 nm.

All polyclonal antibodies showed immunoreactivity to the appropriate antigen.

B) PREPARATION AND CHARACTERIZATION OF ANTIBODIES AGAINST P501S

A murine monoclonal antibody directed against the carboxy-terminus of the prostate-specific antigen P501S was prepared as follows.

A truncated fragment of P501S (amino acids 355-526 of SEQ ID NO: 113) was generated and cloned into the pET28b vector (Novagen) and expressed in *E. coli* as a thioredoxin fusion protein with a histidine tag. The trx-P501S fusion protein was purified by nickel chromatography, digested with thrombin to remove the trx fragment and further purified by an acid precipitation procedure followed by reverse phase HPLC.

Mice were immunized with truncated P501S protein. Serum bleeds from mice that potentially contained anti-P501S polyclonal sera were tested for P501S-specific reactivity using ELISA assays with purified P501S and trx-P501S proteins. Serum bleeds that appeared to react specifically with P501S were then screened for P501S reactivity by Western analysis. Mice that contained a P501S-specific antibody component were

sacrificed and spleen cells were used to generate anti-P501S antibody producing hybridomas using standard techniques. Hybridoma supernatants were tested for P501S-specific reactivity initially by ELISA, and subsequently by FACS analysis of reactivity with P501S transduced cells. Based on these results, a monoclonal hybridoma referred to as 10E3 was chosen for further subcloning. A number of subclones were generated, tested for specific reactivity to P501S using ELISA and typed for IgG isotype. The results of this analysis are shown below in Table V. Of the 16 subclones tested, the monoclonal antibody 10E3-G4-D3 was selected for further study.

10

Table V

Isotype analysis of murine anti-P501S monoclonal antibodies

Hybridoma clone	Isotype	Estimated [Ig] in supernatant (µg/ml)
4D11	IgG1	14.6
1G1	IgG1	0.6
4F6	IgG1	72
4H5	IgG1	13.8
4H5-E12	IgG1	10.7
4H5-EH2	IgG1	9.2
4H5-H2-A10	IgG1	10
4H5-H2-A3	IgG1	12.8
4H5-H2-A10-G6	IgG1	13.6
4H5-H2-B11	IgG1	12.3
10E3	IgG2a	3.4
10E3-D4	IgG2a	3.8
10E3-D4-G3	IgG2a	9.5
10E3-D4-G6	IgG2a	10.4
10E3-E7	IgG2a	6.5
8H12	IgG2a	0.6

The specificity of 10E3-G4-D3 for P501S was examined by FACS analysis. Specifically, cells were fixed (2% formaldehyde, 10 minutes), permeabilized (0.1% saponin, 10 minutes) and stained with 10E3-G4-D3 at 0.5 – 1 µg/ml, followed by incubation with a secondary, FITC-conjugated goat anti-mouse Ig antibody (Pharmingen, San Diego, CA). Cells were then analyzed for FITC fluorescence using an Excalibur

fluorescence activated cell sorter. For FACS analysis of transduced cells, B-LCL were retrovirally transduced with P501S. For analysis of infected cells, B-LCL were infected with a vaccinia vector that expresses P501S. To demonstrate specificity in these assays, B-LCL transduced with a different antigen (P703P) and uninfected B-LCL vectors were
 5 utilized. 10E3-G4-D3 was shown to bind with P501S-transduced B-LCL and also with P501S-infected B-LCL, but not with either uninfected cells or P703P-transduced cells.

To determine whether the epitope recognized by 10E3-G4-D3 was found on the surface or in an intracellular compartment of cells, B-LCL were transduced with P501S or HLA-B8 as a control antigen and either fixed and permeabilized as described above or
 10 directly stained with 10E3-G4-D3 and analyzed as above. Specific recognition of P501S by 10E3-G4-D3 was found to require permeabilization, suggesting that the epitope recognized by this antibody is intracellular.

The reactivity of 10E3-G4-D3 with the three prostate tumor cell lines Lncap, PC-3 and DU-145, which are known to express high, medium and very low levels
 15 of P501S, respectively, was examined by permeabilizing the cells and treating them as described above. Higher reactivity of 10E3-G4-D3 was seen with Lncap than with PC-3, which in turn showed higher reactivity than DU-145. These results are in agreement with the real time PCR and demonstrate that the antibody specifically recognizes P501S in these tumor cell lines and that the epitope recognized in prostate tumor cell lines is also
 20 intracellular.

Specificity of 10E3-G4-D3 for P501S was also demonstrated by Western blot analysis. Lysates from the prostate tumor cell lines Lncap, DU-145 and PC-3, from P501S-transiently transfected HEK293 cells, and from non-transfected HEK293 cells were generated. Western blot analysis of these lysates with 10E3-G4-D3 revealed a 46 kDa
 25 immunoreactive band in Lncap, PC-3 and P501S-transfected HEK cells, but not in DU-145 cells or non-transfected HEK293 cells. P501S mRNA expression is consistent with these results since semi-quantitative PCR analysis revealed that P501S mRNA is expressed in Lncap, to a lesser but detectable level in PC-3 and not at all in DU-145 cells. Bacterially expressed and purified recombinant P501S (referred to as P501SStr2) was recognized by

10E3-G4-D3 (24 kDa), as was full-length P501S that was transiently expressed in HEK293 cells using either the expression vector VR1012 or pCEP4. Although the predicted molecular weight of P501S is 60.5 kDa, both transfected and “native” P501S run at a slightly lower mobility due to its hydrophobic nature.

5 Immunohistochemical analysis was performed on prostate tumor and a panel of normal tissue sections (prostate, adrenal, breast, cervix, colon, duodenum, gall bladder, ileum, kidney, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis). Tissue samples were fixed in formalin solution for 24 hours and embedded in paraffin before being sliced into 10 micron sections. Tissue sections were permeabilized and
10 incubated with 10E3-G4-D3 antibody for 1 hr. HRP-labeled anti-mouse followed by incubation with DAB chromogen was used to visualize P501S immunoreactivity. P501S was found to be highly expressed in both normal prostate and prostate tumor tissue but was not detected in any of the other tissues tested.

To identify the epitope recognized by 10E3-G4-D3, an epitope mapping
15 approach was pursued. A series of 13 overlapping 20-21 mers (5 amino acid overlap; SEQ ID NO: 489-501) was synthesized that spanned the fragment of P501S used to generate 10E3-G4-D3. Flat bottom 96 well microtiter plates were coated with either the peptides or the P501S fragment used to immunize mice, at 1 microgram/ml for 2 hours at 37 °C. Wells were then aspirated and blocked with phosphate buffered saline containing 1% (w/v) BSA
20 for 2 hours at room temperature, and subsequently washed in PBS containing 0.1% Tween 20 (PBST). Purified antibody 10E3-G4-D3 was added at 2 fold dilutions (1000 ng – 16 ng) in PBST and incubated for 30 minutes at room temperature. This was followed by washing 6 times with PBST and subsequently incubating with HRP-conjugated donkey anti-mouse IgG (H+L)Affinipure F(ab') fragment (Jackson ImmunoResearch, West Grove, PA) at
25 1:20000 for 30 minutes. Plates were then washed and incubated for 15 minutes in tetramethyl benzidine. Reactions were stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using an ELISA plate reader. As shown in Fig. 8, reactivity was seen with the peptide of SEQ ID NO: 496 (corresponding to amino acids 439-459 of P501S) and with the P501S fragment but not with the remaining peptides, demonstrating

that the epitope recognized by 10E3-G4-D3 is localized to amino acids 439-459 of SEQ ID NO: 113.

In order to further evaluate the tissue specificity of P501S, multi-array immunohistochemical analysis was performed on approximately 4700 different human tissues encompassing all the major normal organs as well as neoplasias derived from these tissues. Sixty-five of these human tissue samples were of prostate origin. Tissue sections 0.6 mm in diameter were formalin-fixed and paraffin embedded. Samples were pretreated with HIER using 10 mM citrate buffer pH 6.0 and boiling for 10 min. Sections were stained with 10E3-G4-D3 and P501S immunoreactivity was visualized with HRP. All the 65 prostate tissues samples (5 normal, 55 untreated prostate tumors, 5 hormone refractory prostate tumors) were positive, showing distinct perinuclear staining. All other tissues examined were negative for P501S expression.

C) PREPARATION AND CHARACTERIZATION OF ANTIBODIES AGAINST P503S

A fragment of P503S (amino acids 113-241 of SEQ ID NO: 114) was expressed and purified from bacteria essentially as described above for P501S and used to immunize both rabbits and mice. Mouse monoclonal antibodies were isolated using standard hybridoma technology as described above. Rabbit monoclonal antibodies were isolated using Selected Lymphocyte Antibody Method (SLAM) technology at Immgenics Pharmaceuticals (Vancouver, BC, Canada). Table VI, below, lists the monoclonal antibodies that were developed against P503S.

Table VI

Antibody	Species
20D4	Rabbit
JA1	Rabbit
1A4	Mouse
1C3	Mouse
1C9	Mouse
1D12	Mouse

Antibody	Species
2A11	Mouse
2H9	Mouse
4H7	Mouse
8A8	Mouse
8D10	Mouse
9C12	Mouse
6D12	Mouse

The DNA sequences encoding the complementarity determining regions (CDRs) for the rabbit monoclonal antibodies 20D4 and JA1 were determined and are provided in SEQ ID NO: 502 and 503, respectively.

5 In order to better define the epitope binding region of each of the antibodies, a series of overlapping peptides were generated that span amino acids 109-213 of SEQ ID NO: 114. These peptides were used to epitope map the anti-P503S monoclonal antibodies by ELISA as follows. The recombinant fragment of P503S that was employed as the immunogen was used as a positive control. Ninety-six well microtiter plates were coated
10 with either peptide or recombinant antigen at 20 ng/well overnight at 4 °C. Plates were aspirated and blocked with phosphate buffered saline containing 1% (w/v) BSA for 2 hours at room temperature then washed in PBS containing 0.1% Tween 20 (PBST). Purified rabbit monoclonal antibodies diluted in PBST were added to the wells and incubated for 30 min at room temperature. This was followed by washing 6 times with PBST and
15 incubation with Protein-A HRP conjugate at a 1:2000 dilution for a further 30 min. Plates were washed six times in PBST and incubated with tetramethylbenzidine (TMB) substrate for a further 15 min. The reaction was stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using at ELISA plate reader. ELISA with the mouse monoclonal antibodies was performed with supernatants from tissue culture run neat in the
20 assay.

All of the antibodies bound to the recombinant P503S fragment, with the exception of the negative control SP2 supernatant. 20D4, JA1 and 1D12 bound strictly to peptide #2101 (SEQ ID NO: 504), which corresponds to amino acids 151-169 of SEQ ID

NO: 114. 1C3 bound to peptide #2102 (SEQ ID NO: 505), which corresponds to amino acids 165-184 of SEQ ID NO: 114. 9C12 bound to peptide #2099 (SEQ ID NO: 522), which corresponds to amino acids 120-139 of SEQ ID NO: 114. The other antibodies bind to regions that were not examined in these studies.

5 Subsequent to epitope mapping, the antibodies were tested by FACS analysis on a cell line that stably expressed P503S to confirm that the antibodies bind to cell surface epitopes. Cells stably transfected with a control plasmid were employed as a negative control. Cells were stained live with no fixative. 0.5 ug of anti-P503S monoclonal antibody was added and cells were incubated on ice for 30 min before being
10 washed twice and incubated with a FITC-labelled goat anti-rabbit or mouse secondary antibody for 20 min. After being washed twice, cells were analyzed with an Excalibur fluorescent activated cell sorter. The monoclonal antibodies 1C3, 1D12, 9C12, 20D4 and JA1, but not 8D3, were found to bind to a cell surface epitope of P503S.

 In order to determine which tissues express P503S, immunohistochemical
15 analysis was performed, essentially as described above, on a panel of normal tissues (prostate, adrenal, breast, cervix, colon, duodenum, gall bladder, ileum, kidney, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis). HRP-labeled anti-mouse or anti-rabbit antibody followed by incubation with TMB was used to visualize P503S immunoreactivity. P503S was found to be highly expressed in prostate tissue, with lower
20 levels of expression being observed in cervix, colon, ileum and kidney, and no expression being observed in adrenal, breast, duodenum, gall bladder, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis.

 Western blot analysis was used to characterize anti-P503S monoclonal antibody specificity. SDS-PAGE was performed on recombinant (rec) P503S expressed in
25 and purified from bacteria and on lysates from HEK293 cells transfected with full length P503S. Protein was transferred to nitrocellulose and then Western blotted with each of the anti-P503S monoclonal antibodies (20D4, JA1, 1D12, 6D12 and 9C12) at an antibody concentration of 1 ug/ml. Protein was detected using horse radish peroxidase (HRP) conjugated to either a goat anti-mouse monoclonal antibody or to protein A-sepharose.

The monoclonal antibody 20D4 detected the appropriate molecular weight 14 kDa recombinant P503S (amino acids 113-241) and the 23.5 kDa species in the HEK293 cell lysates transfected with full length P503S. Other anti-P503S monoclonal antibodies displayed similar specificity by Western blot.

5 **D) PREPARATION AND CHARACTERIZATION OF ANTIBODIES AGAINST P703P**

Rabbits were immunized with either a truncated (P703Ptr1; SEQ ID NO: 172) or full-length mature form (P703Pfl; SEQ ID NO: 523) of recombinant P703P protein was expressed in and purified from bacteria as described above. Affinity purified polyclonal antibody was generated using immunogen P703Pfl or P703Ptr1 attached to a solid support. Rabbit monoclonal antibodies were isolated using SLAM technology at Immgenics Pharmaceuticals. Table VII below lists both the polyclonal and monoclonal antibodies that were generated against P703P.

Table VII

Antibody	Immunogen	Species/type
Aff. Purif. P703P (truncated); #2594	P703Ptrl	Rabbit polyclonal
Aff. Purif. P703P (full length); #9245	P703Pfl	Rabbit polyclonal
2D4	P703Ptrl	Rabbit monoclonal
8H2	P703Ptrl	Rabbit monoclonal
7H8	P703Ptrl	Rabbit monoclonal

The DNA sequences encoding the complementarity determining regions (CDRs) for the rabbit monoclonal antibodies 8H2, 7H8 and 2D4 were determined and are provided in SEQ ID NO: 506-508, respectively.

Epitope mapping studies were performed as described above. Monoclonal antibodies 2D4 and 7H8 were found to specifically bind to the peptides of SEQ ID NO: 509 (corresponding to amino acids 145-159 of SEQ ID NO: 172) and SEQ ID NO: 510 (corresponding to amino acids 11-25 of SEQ ID NO: 172), respectively. The polyclonal

antibody 2594 was found to bind to the peptides of SEQ ID NO: 511-514, with the polyclonal antibody 9427 binding to the peptides of SEQ ID NO: 515-517.

The specificity of the anti-P703P antibodies was determined by Western blot analysis as follows. SDS-PAGE was performed on (1) bacterially expressed recombinant antigen; (2) lysates of HEK293 cells and Ltk^{-/-} cells either untransfected or transfected with a plasmid expressing full length P703P; and (3) supernatant isolated from these cell cultures. Protein was transferred to nitrocellulose and then Western blotted using the anti-P703P polyclonal antibody #2594 at an antibody concentration of 1 ug/ml. Protein was detected using horse radish peroxidase (HRP) conjugated to an anti-rabbit antibody. A 35 kDa immunoreactive band could be observed with recombinant P703P. Recombinant P703P runs at a slightly higher molecular weight since it is epitope tagged. In lysates and supernatants from cells transfected with full length P703P, a 30 kDa band corresponding to P703P was observed. To assure specificity, lysates from HEK293 cells stably transfected with a control plasmid were also tested and were negative for P703P expression. Other anti-P703P antibodies showed similar results.

Immunohistochemical studies were performed as described above, using anti-P703P monoclonal antibody. P703P was found to be expressed at high levels in normal prostate and prostate tumor tissue but was not detectable in all other tissues tested (breast tumor, lung tumor and normal kidney).

EXAMPLE 19

CHARACTERIZATION OF CELL SURFACE EXPRESSION AND CHROMOSOME LOCALIZATION OF THE PROSTATE-SPECIFIC ANTIGEN P501S

This example describes studies demonstrating that the prostate-specific antigen P501S is expressed on the surface of cells, together with studies to determine the probable chromosomal location of P501S.

The protein P501S (SEQ ID NO: 113) is predicted to have 11 transmembrane domains. Based on the discovery that the epitope recognized by the anti-

P501S monoclonal antibody 10E3-G4-D3 (described above in Example 17) is intracellular, it was predicted that following transmembrane determinants would allow the prediction of extracellular domains of P501S. Fig. 9 is a schematic representation of the P501S protein showing the predicted location of the transmembrane domains and the intracellular epitope described in Example 17. Underlined sequence represents the predicted transmembrane domains, bold sequence represents the predicted extracellular domains, and italicized sequence represents the predicted intracellular domains. Sequence that is both bold and underlined represents sequence employed to generate polyclonal rabbit serum. The location of the transmembrane domains was predicted using HHMTOP as described by Tusnady and Simon (Principles Governing Amino Acid Composition of Integral Membrane Proteins: Applications to Topology Prediction, *J. Mol. Biol.* 283:489-506, 1998).

Based on Fig. 9, the P501S domain flanked by the transmembrane domains corresponding to amino acids 274-295 and 323-342 is predicted to be extracellular. The peptide of SEQ ID NO: 518 corresponds to amino acids 306-320 of P501S and lies in the predicted extracellular domain. The peptide of SEQ ID NO: 519, which is identical to the peptide of SEQ ID NO: 518 with the exception of the substitution of the histidine with an asparagine, was synthesized as described above. A Cys-Gly was added to the C-terminus of the peptide to facilitate conjugation to the carrier protein. Cleavage of the peptide from the solid support was carried out using the following cleavage mixture: trifluoroacetic acid:ethanediol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for two hours, the peptide was precipitated in cold ether. The peptide pellet was then dissolved in 10% v/v acetic acid and lyophilized prior to purification by C18 reverse phase hplc. A gradient of 5-60% acetonitrile (containing 0.05% TFA) in water (containing 0.05% TFA) was used to elute the peptide. The purity of the peptide was verified by hplc and mass spectrometry, and was determined to be >95%. The purified peptide was used to generate rabbit polyclonal antisera as described above.

Surface expression of P501S was examined by FACS analysis. Cells were stained with the polyclonal anti-P501S peptide serum at 10 µg/ml, washed, incubated with

a secondary FITC-conjugated goat anti-rabbit Ig antibody (ICN), washed and analyzed for FITC fluorescence using an Excalibur fluorescence activated cell sorter. For FACS analysis of transduced cells, B-LCL were retrovirally transduced with P501S. To demonstrate specificity in these assays, B-LCL transduced with an irrelevant antigen (P703P) or nontransduced were stained in parallel. For FACS analysis of prostate tumor cell lines, Lncap, PC-3 and DU-145 were utilized. Prostate tumor cell lines were dissociated from tissue culture plates using cell dissociation medium and stained as above. All samples were treated with propidium iodide (PI) prior to FACS analysis, and data was obtained from PI-excluding (*i.e.*, intact and non-permeabilized) cells. The rabbit polyclonal serum generated against the peptide of SEQ ID NO: 519 was shown to specifically recognize the surface of cells transduced to express P501S, demonstrating that the epitope recognized by the polyclonal serum is extracellular.

To determine biochemically if P501S is expressed on the cell surface, peripheral membranes from Lncap cells were isolated and subjected to Western blot analysis. Specifically, Lncap cells were lysed using a dounce homogenizer in 5 ml of homogenization buffer (250 mM sucrose, 10 mM HEPES, 1mM EDTA, pH 8.0, 1 complete protease inhibitor tablet (Boehringer Mannheim)). Lysate samples were spun at 1000 g for 5 min at 4 °C. The supernatant was then spun at 8000g for 10 min at 4 °C. Supernatant from the 8000g spin was recovered and subjected to a 100,000g spin for 30 min at 4 °C to recover peripheral membrane. Samples were then separated by SDS-PAGE and Western blotted with the mouse monoclonal antibody 10E3-G4-D3 (described above in Example 17) using conditions described above. Recombinant purified P501S, as well as HEK293 cells transfected with and over-expressing P501S were included as positive controls for P501S detection. LCL cell lysate was included as a negative control. P501S could be detected in Lncap total cell lysate, the 8000g (internal membrane) fraction and also in the 100,000g (plasma membrane) fraction. These results indicate that P501S is expressed at, and localizes to, the peripheral membrane.

To demonstrate that the rabbit polyclonal antiserum generated to the peptide of SEQ ID NO: 519 specifically recognizes this peptide as well as the corresponding native

peptide of SEQ ID NO: 518, ELISA analyses were performed. For these analyses, flat-bottomed 96 well microtiter plates were coated with either the peptide of SEQ ID NO: 519, the longer peptide of SEQ ID NO: 520 that spans the entire predicted extracellular domain, the peptide of SEQ ID NO: 521 which represents the epitope recognized by the P501S-specific antibody 10E3-G4-D3, or a P501S fragment (corresponding to amino acids 355-526 of SEQ ID NO: 113) that does not include the immunizing peptide sequence, at 1 µg/ml for 2 hours at 37 °C. Wells were aspirated, blocked with phosphate buffered saline containing 1% (w/v) BSA for 2 hours at room temperature and subsequently washed in PBS containing 0.1% Tween 20 (PBST). Purified anti-P501S polyclonal rabbit serum was added at 2 fold dilutions (1000 ng - 125 ng) in PBST and incubated for 30 min at room temperature. This was followed by washing 6 times with PBST and incubating with HRP-conjugated goat anti-rabbit IgG (H+L) Affinipure F(ab') fragment at 1:20000 for 30 min. Plates were then washed and incubated for 15 min in tetramethyl benzidine. Reactions were stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using an ELISA plate reader. As shown in Fig. 11, the anti-P501S polyclonal rabbit serum specifically recognized the peptide of SEQ ID NO: 519 used in the immunization as well as the longer peptide of SEQ ID NO: 520, but did not recognize the irrelevant P501S-derived peptides and fragments.

In further studies, rabbits were immunized with peptides derived from the P501S sequence and predicted to be either extracellular or intracellular, as shown in Fig. 9. Polyclonal rabbit sera were isolated and polyclonal antibodies in the serum were purified, as described above. To determine specific reactivity with P501S, FACS analysis was employed, utilizing either B-LCL transduced with P501S or the irrelevant antigen P703P, of B-LCL infected with vaccinia virus-expressing P501S. For surface expression, dead and non-intact cells were excluded from the analysis as described above. For intracellular staining, cells were fixed and permeabilized as described above. Rabbit polyclonal serum generated against the peptide of SEQ ID NO: 548, which corresponds to amino acids 181-198 of P501S, was found to recognize a surface epitope of P501S. Rabbit polyclonal serum generated against the peptide SEQ ID NO: 551, which corresponds to amino acids

543-553 of P501S, was found to recognize an epitope that was either potentially extracellular or intracellular since in different experiments intact or permeabilized cells were recognized by the polyclonal sera. Based on similar deductive reasoning, the sequences of SEQ ID NO: 541-547, 549 and 550, which correspond to amino acids 109-122, 539-553, 509-520, 37-54, 342-359, 295-323, 217-274, 143-160 and 75-88, respectively, of P501S, can be considered to be potential surface epitopes of P501S recognized by antibodies.

The chromosomal location of P501S was determined using the GeneBridge 4 Radiation Hybrid panel (Research Genetics). The PCR primers of SEQ ID NO: 528 and 529 were employed in PCR with DNA pools from the hybrid panel according to the manufacturer's directions. After 38 cycles of amplification, the reaction products were separated on a 1.2% agarose gel, and the results were analyzed through the Whitehead Institute/MIT Center for Genome Research web server (<http://www-genome.wi.mit.edu/cgi-bin/contig/rhmapper.pl>) to determine the probable chromosomal location. Using this approach, P501S was mapped to the long arm of chromosome 1 at WI-9641 between q32 and q42. This region of chromosome 1 has been linked to prostate cancer susceptibility in hereditary prostate cancer (Smith *et al. Science* 274:1371-1374, 1996 and Berthon *et al. Am. J. Hum. Genet.* 62:1416-1424, 1998). These results suggest that P501S may play a role in prostate cancer malignancy.

EXAMPLE 20

REGULATION OF EXPRESSION OF THE PROSTATE-SPECIFIC ANTIGEN P501S

Steroid (androgen) hormone modulation is a common treatment modality in prostate cancer. The expression of a number of prostate tissue-specific antigens have previously been demonstrated to respond to androgen. The responsiveness of the prostate-specific antigen P501S to androgen treatment was examined in a tissue culture system as follows.

Cells from the prostate tumor cell line LNCaP were plated at 1.5×10^6 cells/T75 flask (for RNA isolation) or 3×10^5 cells/well of a 6-well plate (for FACS analysis) and grown overnight in RPMI 1640 media containing 10% charcoal-stripped fetal calf serum (BRL Life Technologies, Gaithersburg, MD). Cell culture was continued for an additional 72 hours in RPMI 1640 media containing 10% charcoal-stripped fetal calf serum, with 1 nM of the synthetic androgen Methyltrienolone (R1881; New England Nuclear) added at various time points. Cells were then harvested for RNA isolation and FACS analysis at 0, 1, 2, 4, 8, 16, 24, 28 and 72-hours post androgen addition. FACS analysis was performed using the anti-P501S antibody 10E3-G4-D3 and permeabilized cells.

For Northern analysis, 5-10 micrograms of total RNA was run on a formaldehyde denaturing gel, transferred to Hybond-N nylon membrane (Amersham Pharmacia Biotech, Piscataway, NJ), cross-linked and stained with methylene blue. The filter was then prehybridized with Church's Buffer (250 mM Na_2HPO_4 , 70 mM H_3PO_4 , 1 mM EDTA, 1% SDS, 1% BSA in pH 7.2) at 65 °C for 1 hour. P501S DNA was labeled with ^{32}P using High Prime random-primed DNA labeling kit (Boehringer Mannheim). Unincorporated label was removed using MicroSpin S300-HR columns (Amersham Pharmacia Biotech). The RNA filter was then hybridized with fresh Church's Buffer containing labeled cDNA overnight, washed with 1X SCP (0.1 M NaCl, 0.03 M $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$, 0.001 M Na_2EDTA), 1% sarkosyl (n-lauroylsarcosine) and exposed to X-ray film.

Using both FACS and Northern analysis, P501S message and protein levels were found to increase in response to androgen treatment.

25

EXAMPLE 20

PREPARATION OF FUSION PROTEINS OF PROSTATE-SPECIFIC ANTIGENS

The example describes the preparation of a fusion protein of the prostate-specific antigen P703P and a truncated form of the known prostate antigen PSA. The

truncated form of PSA has a 21 amino acid deletion around the active serine site. The expression construct for the fusion protein also has a restriction site at 3' end, immediately prior to the termination codon, to aid in adding cDNA for additional antigens.

The full-length cDNA for PSA was obtained by RT-PCR from a pool of
 5 RNA from human prostate tumor tissues using the primers of SEQ ID NO: 607 and 608, and cloned in the vector pCR-Blunt II-TOPO. The resulting cDNA was employed as a template to make two different fragments of PSA by PCR with two sets of primers (SEQ ID NO: 609 and 610; and SEQ ID NO: 611 and 612). The PCR products having the expected size were used as templates to make truncated forms of PSA by PCR with the
 10 primers of SEQ ID NO: 611 and 613, which generated PSA (delta 208-218 in amino acids). The cDNA for the mature form of P703P with a 6X histidine tag at the 5' end, was prepared by PCR with P703P and the primers of SEQ ID NO: 614 and 615. The cDNA for the fusion of P703P with the truncated form of PSA (referred to as FOPP) was then obtained by PCR using the modified P703P cDNA and the truncated form of PSA cDNA
 15 as templates and the primers of SEQ ID NO: 614 and 615. The FOPP cDNA was cloned into the NdeI site and XhoI site of the expression vector pCRX1, and confirmed by DNA sequencing. The determined cDNA sequence for the fusion construct FOPP is provided in SEQ ID NO: 616, with the amino acid sequence being provided in SEQ ID NO: 617.

The fusion FOPP was expressed as a single recombinant protein in *E. coli* as
 20 follows. The expression plasmid pCRX1FOPP was transformed into the *E. coli* strain BL21-CodonPlus RIL. The transformant was shown to express FOPP protein upon induction with 1 mM IPTG. The culture of the corresponding expression clone was inoculated into 25 ml LB broth containing 50 ug/ml kanamycin and 34 ug/ml chloramphenicol, grown at 37 °C to OD600 of about 1, and stored at 4 °C overnight. The
 25 culture was diluted into 1 liter of TB LB containing 50 ug/ml kanamycin and 34 ug/ml chloramphenicol, and grown at 37 °C to OD600 of 0.4. IPTG was added to a final concentration of 1 mM, and the culture was incubated at 30 °C for 3 hours. The cells were pelleted by centrifugation at 5,000 RPM for 8 min. To purify the protein, the cell pellet was suspended in 25 ml of 10 mM Tris-Cl pH 8.0, 2mM PMSF, complete protease

inhibitor and 15 ug lysozyme. The cells were lysed at 4 °C for 30 minutes, sonicated several times and the lysate centrifuged for 30 minutes at 10,000 x g. The precipitate, which contained the inclusion body, was washed twice with 10 mM Tris-Cl pH 8.0 and 1% CHAPS. The inclusion body was dissolved in 40 ml of 10 mM Tris-Cl pH 8.0, 100 mM sodium phosphate and 8 M urea. The solution was bound to 8 ml Ni-NTA (Qiagen) for one hour at room temperature. The mixture was poured into a 25 ml column and washed with 50 ml of 10 mM Tris-Cl pH 6.3, 100 mM sodium phosphate, 0.5% DOC and 8M urea. The bound protein was eluted with 350 mM imidazole, 10 mM Tris-Cl pH 8.0, 100 mM sodium phosphate and 8 M urea. The fractions containing FOPP proteins were combined and dialyzed extensively against 10 mM Tris-Cl pH 4.6, aliquoted and stored at - 70 °C.

EXAMPLE 21

REAL-TIME PCR CHARACTERIZATION OF THE PROSTATE-SPECIFIC ANTIGEN P501S IN PERIPHERAL BLOOD OF PROSTATE CANCER PATIENTS

Circulating epithelial cells were isolated from fresh blood of normal individuals and metastatic prostate cancer patients, mRNA isolated and cDNA prepared using real-time PCR procedures. Real-time PCR was performed with the TaqmanTM procedure using both gene specific primers and probes to determine the levels of gene expression.

Epithelial cells were enriched from blood samples using an immunomagnetic bead separation method (Dynal A.S., Oslo, Norway). Isolated cells were lysed and the magnetic beads removed. The lysate was then processed for poly A+ mRNA isolation using magnetic beads coated with Oligo(dT)25. After washing the beads in buffer, bead/poly A+ RNA samples were suspended in 10 mM Tris HCl pH 8.0 and subjected to reversed transcription. The resulting cDNA was subjected to real-time PCR using gene specific primers. Beta-actin content was also determined and used for normalization. Samples with P501S copies greater than the mean of the normal samples + 3 standard deviations were considered positive. Real time PCR on blood samples was

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10 claims.

CLAIMS

What is claimed:

1. An isolated polypeptide, comprising at least an immunogenic portion of a prostate-specific protein, wherein the protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772, 779, 817, 823 and 824;

(b) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772, 779, 817, 823 and 824 under moderately stringent conditions; and

(c) complements of sequences of (a) or (b).

2. An isolated polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434,

435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772, 779, 817, 823 and 824, or a complement of any of the foregoing polynucleotide sequences.

3. An isolated polypeptide comprising a sequence recited in any one of SEQ ID NO: 108, 112, 113, 114, 172, 176, 178, 327, 329, 331, 338, 339, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 706-708, 778, 780, 781, 810, 811, 814, 818, 826 and 827.

4. An isolated polynucleotide encoding at least 15 amino acid residues of a prostate-specific protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NO: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772, 779, 817, 823 and 824, or a complement of any of the foregoing sequences.

5. An isolated polynucleotide encoding a prostate-specific protein, or a variant thereof, wherein the protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-

461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772, 779, 817, 823 and 824, or a complement of any of the foregoing sequences.

6. An isolated polynucleotide, comprising a sequence recited in any one of SEQ ID NO: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772, 779, 817, 823 and 824.

7. An isolated polynucleotide, comprising a sequence that hybridizes to a sequence recited in any one of SEQ ID NO: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772, 779, 817, 823 and 824 under moderately stringent conditions.

8. An isolated polynucleotide complementary to a polynucleotide according to any one of claims 4-7.

9. An expression vector, comprising a polynucleotide according to any one of claims 4-8.

10. A host cell transformed or transfected with an expression vector according to claim 9.

11. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a prostate-specific protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772, 779, 817, 823 and 824, or a complement of any of the foregoing polynucleotide sequences.

12. A fusion protein, comprising at least one polypeptide according to claim 1.

13. A fusion protein according to claim 12, wherein the fusion protein comprises an expression enhancer that increases expression of the fusion protein in a host cell transfected with a polynucleotide encoding the fusion protein.

14. A fusion protein according to claim 12, wherein the fusion protein comprises a T helper epitope that is not present within the polypeptide of claim 1.

15. A fusion protein according to claim 12, wherein the fusion protein comprises an affinity tag.

16. An isolated polynucleotide encoding a fusion protein according to claim 12.

17. A pharmaceutical composition, comprising a physiologically acceptable carrier and at least one component selected from the group consisting of:

(a) a polypeptide according to claim 1;

- (b) a polynucleotide according to claim 4;
- (c) an antibody according to claim 11;
- (d) a fusion protein according to claim 12; and
- (e) a polynucleotide according to claim 16.

18. An immunogenic composition comprising an immunostimulant and at least one component selected from the group consisting of:

- (a) a polypeptide according to claim 1;
- (b) a polynucleotide according to claim 4;
- (c) an antibody according to claim 11;
- (d) a fusion protein according to claim 12; and
- (e) a polynucleotide according to claim 16.

19. An immunogenic composition according to claim 18, wherein the immunostimulant is an adjuvant.

20. An immunogenic composition according to claim 18, wherein the immunostimulant induces a predominantly Type I response.

21. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a pharmaceutical composition according to claim 17.

22. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an immunogenic composition according to claim 18.

23. A pharmaceutical composition comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a pharmaceutically acceptable carrier or excipient.

24. A pharmaceutical composition according to claim 23, wherein the antigen presenting cell is a dendritic cell or a macrophage.

25. An immunogenic composition comprising an antigen-presenting cell that expresses a polypeptide comprising at least an immunogenic portion of a prostate-specific protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777, 789, 817, 823 and 824;

(b) sequences that hybridize to a sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777, 789, 817, 823 and 824 under moderately stringent conditions; and

(c) complements of sequences of (i) or (ii);
in combination with an immunostimulant.

26. An immunogenic composition according to claim 25, wherein the immunostimulant is an adjuvant.

27. An immunogenic composition according to claim 25, wherein the immunostimulant induces a predominantly Type I response.

28. An immunogenic composition according to claim 25, wherein the antigen-presenting cell is a dendritic cell.

29. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antigen-presenting cell that expresses a polypeptide comprising at least an immunogenic portion of a prostate-specific protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777, 789, 817, 823 and 824;

(b) sequences that hybridize to a sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777, 789, 817, 823 and 824 under moderately stringent conditions; and

(c) complements of sequences of (i) or (ii) encoded by a polynucleotide recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777, 789, 817, 823 and 824;

and thereby inhibiting the development of a cancer in the patient.

30. A method according to claim 29, wherein the antigen-presenting cell is a dendritic cell.

31. A method according to any one of claims 21, 22 and 29, wherein the cancer is prostate cancer.

32. A method for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a prostate-specific protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) polynucleotides recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777, 789, 817, 823 and 824; and

(ii) complements of the foregoing polynucleotides;

wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the antigen from the sample.

33. A method according to claim 32, wherein the biological sample is blood or a fraction thereof.

34. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated according to the method of claim 32.

35. A method for stimulating and/or expanding T cells specific for a prostate-specific protein, comprising contacting T cells with at least one component selected from the group consisting of:

(a) polypeptides comprising at least an immunogenic portion of a prostate-specific protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) sequences recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777, 789, 817, 823 and 824;

(ii) sequences that hybridize to a sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777, 789, 817, 823 and 824 under moderately stringent conditions; and

(iii) complements of sequences of (i) or (ii);

- (b) polynucleotides encoding a polypeptide of (a); and
- (c) antigen presenting cells that express a polypeptide of (a);

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

36. An isolated T cell population, comprising T cells prepared according to the method of claim 35.

37. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population according to claim 36.

38. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

(a) incubating CD4⁺ and/or CD8⁺ T cells isolated from a patient with at least one component selected from the group consisting of:

(i) polypeptides comprising at least an immunogenic portion of a prostate-specific protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(1) sequences recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777, 789, 817, 823 and 824;

(2) sequences that hybridize to a sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777, 789, 817, 823 and 824 under moderately stringent conditions; and

(3) complements of sequences of (1) or (2);

(ii) polynucleotides encoding a polypeptide of (i); and

(iii) antigen presenting cells that expresses a polypeptide of (i);
such that T cells proliferate; and

(b) administering to the patient an effective amount of the proliferated T cells,
and thereby inhibiting the development of a cancer in the patient.

39. A method for inhibiting the development of a cancer in a patient,
comprising the steps of:

(a) incubating CD4⁺ and/or CD8⁺ T cells isolated from a patient with at least
one component selected from the group consisting of:

(i) polypeptides comprising at least an immunogenic portion of a
prostate-specific protein, or a variant thereof, wherein the tumor protein comprises an amino acid
sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(1) sequences recited in SEQ ID NO: 1-111, 115-171, 173-175,
177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530,
531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777, 789, 817, 823 and
824;

(2) sequences that hybridize to a sequence recited in any one of
SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375,
381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-
705, 709-774, 777, 789, 817, 823 and 824 under moderately stringent conditions; and

(3) complements of sequences of (1) or (2);

(ii) polynucleotides encoding a polypeptide of (i); and

(iii) antigen presenting cells that express a polypeptide of (i);

such that T cells proliferate;

(b) cloning at least one proliferated cell to provide cloned T cells; and

(c) administering to the patient an effective amount of the cloned T cells, and
thereby inhibiting the development of a cancer in the patient.

40. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:

- (a) contacting a biological sample obtained from a patient with a binding agent that binds to a prostate-specific protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777, 789, 817, 823 and 824 or a complement of any of the foregoing polynucleotide sequences;
- (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (c) comparing the amount of polypeptide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

41. A method according to claim 40, wherein the binding agent is an antibody.

42. A method according to claim 43, wherein the antibody is a monoclonal antibody.

43. A method according to claim 40, wherein the cancer is prostate cancer.

44. A method for monitoring the progression of a cancer in a patient, comprising the steps of:

- (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a prostate-specific protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777, 789, 817, 823 and 824 or a complement of any of the foregoing polynucleotide sequences;

- (b) detecting in the sample an amount of polypeptide that binds to the binding agent;
- (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and
- (d) comparing the amount of polypeptide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

45. A method according to claim 44, wherein the binding agent is an antibody.

46. A method according to claim 45, wherein the antibody is a monoclonal antibody.

47. A method according to claim 44, wherein the cancer is a prostate cancer.

48. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate-specific protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777, 789, 817, 823 and 824, or a complement of any of the foregoing polynucleotide sequences;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and

(c) comparing the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

49. A method according to claim 48, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.

50. A method according to claim 48, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.

51. A method for monitoring the progression of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate-specific protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-705, 709-774, 777, 789, 817, 823 and 824, or a complement of any of the foregoing polynucleotide sequences;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide;

(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

52. A method according to claim 51, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.

53. A method according to claim 51, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.

54. A diagnostic kit, comprising:

- (a) one or more antibodies according to claim 11; and
- (b) a detection reagent comprising a reporter group.

55. A kit according to claim 54, wherein the antibodies are immobilized on a solid support.

56. A kit according to claim 54, wherein the detection reagent comprises an anti-immunoglobulin, protein G, protein A or lectin.

57. A kit according to claim 54, wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.

58. An oligonucleotide comprising 10 to 40 contiguous nucleotides that hybridize under moderately stringent conditions to a polynucleotide that encodes a prostate-specific protein, wherein the protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772, 779, 817, 823 and 824, or a complement of any of the foregoing polynucleotides.

59. A oligonucleotide according to claim 58, wherein the oligonucleotide comprises 10-40 contiguous nucleotides recited in any one of SEQ ID NO: 2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326,

328, 330, 332, 334, 350-361, 363-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471, 472-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-689, 691-698, 702-705, 709-772, 779, 817, 823 and 824.

60. A diagnostic kit, comprising:

- (a) an oligonucleotide according to claim 59; and
- (b) a diagnostic reagent for use in a polymerase chain reaction or hybridization assay.

61. A fusion protein according to claim 12, wherein the fusion protein comprises an amino acid sequence selected from the group consisting of: SEQ ID NO: 617, 825 and 835.

63. A fusion protein according to claim 12, wherein the fusion protein comprises an amino acid sequence encoded by a sequence selected from the group consisting of: SEQ ID NO: 616, 822 and 834.

COMPOSITIONS AND METHODS FOR THE THERAPY
AND DIAGNOSIS OF PROSTATE CANCER

ABSTRACT OF THE DISCLOSURE

Compositions and methods for the therapy and diagnosis of cancer, such as prostate cancer, are disclosed. Compositions may comprise one or more prostate-specific proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses a prostate-specific protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as prostate cancer. Diagnostic methods based on detecting a prostate-specific protein, or mRNA encoding such a protein, in a sample are also provided.

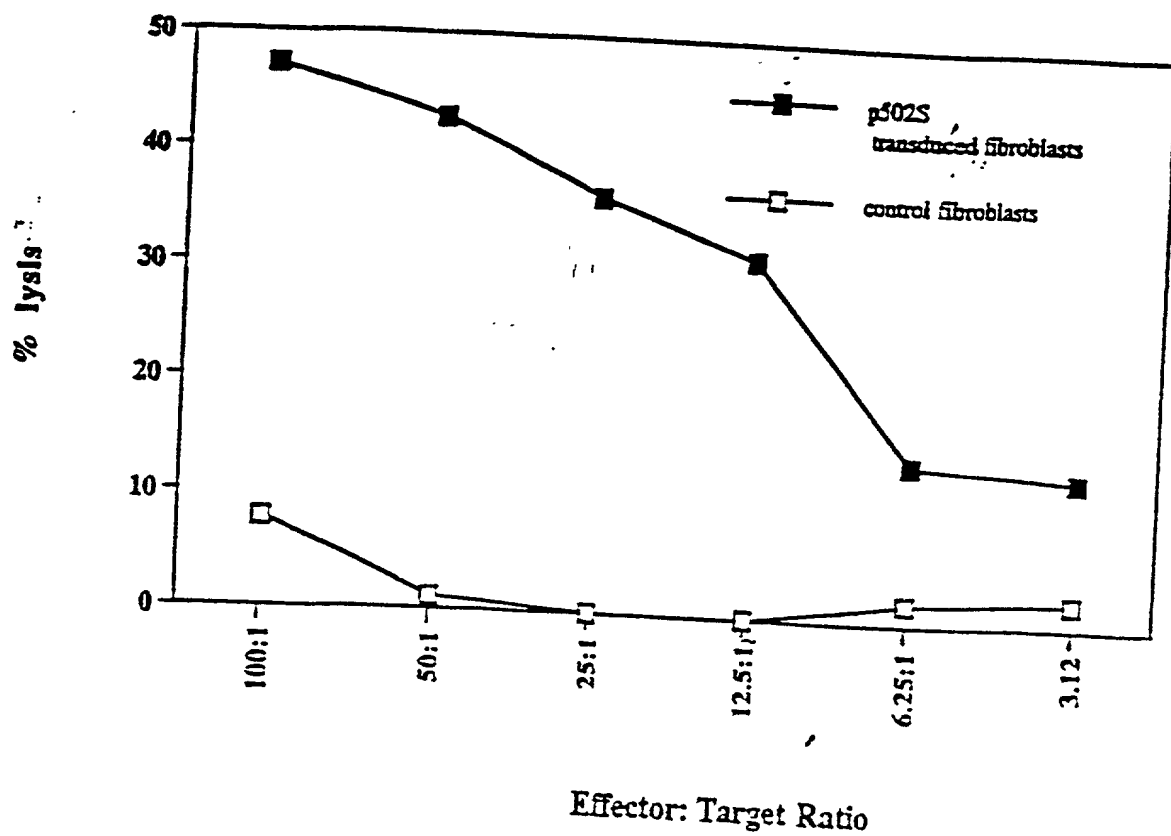


FIG. 1

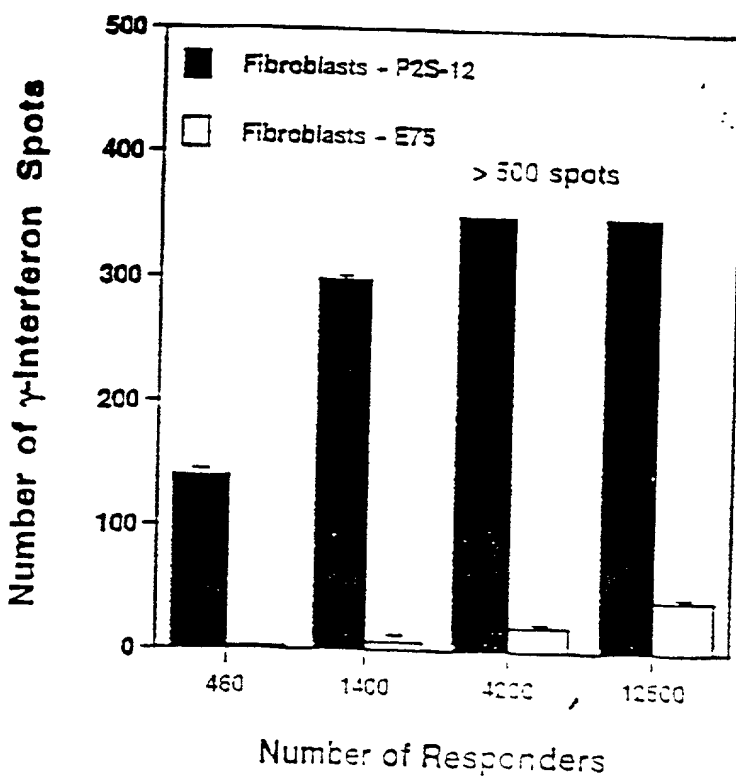


FIG. 2.4

002390-28250960

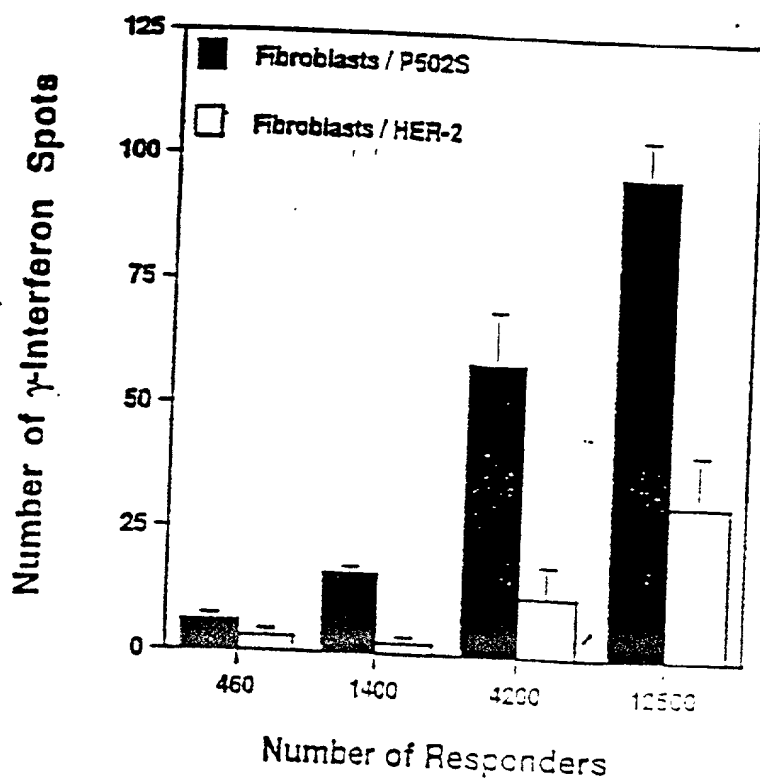


FIG. 2B

002690-28/50960

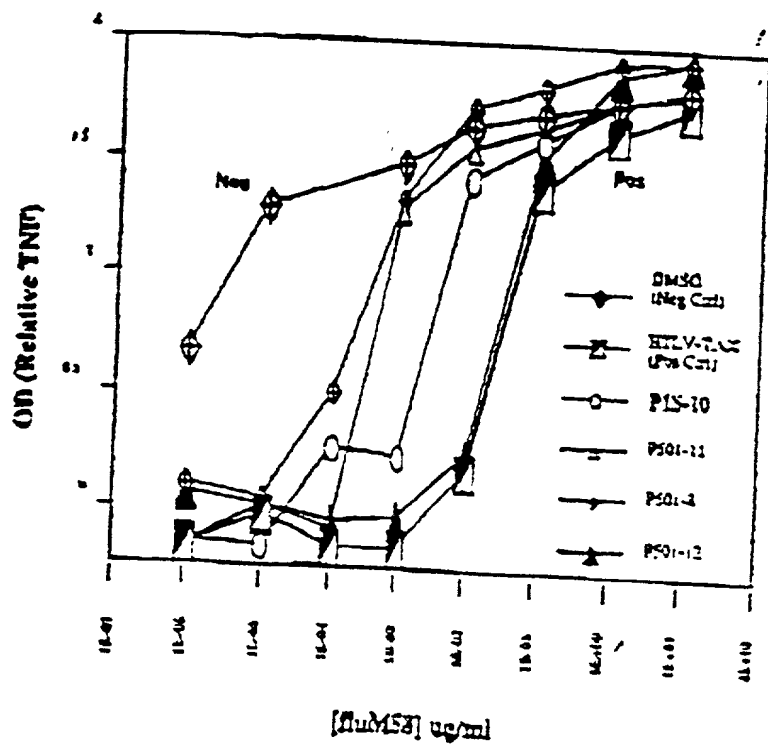


Figure 3

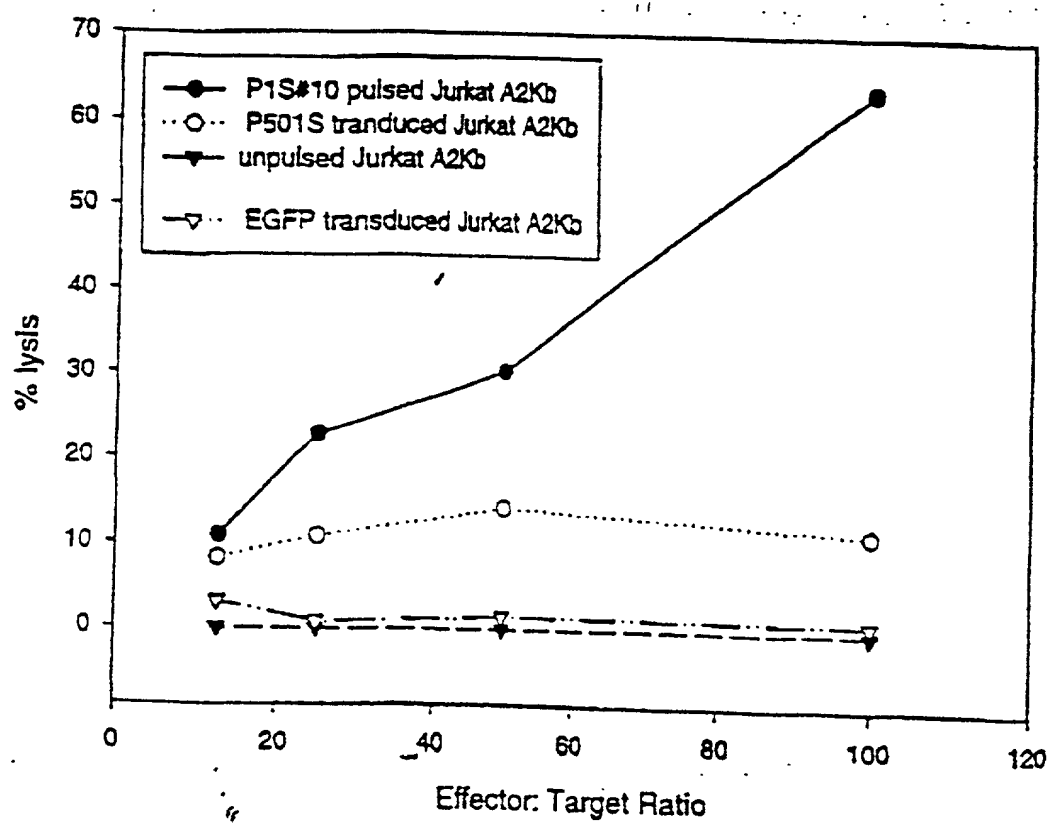


Figure 4

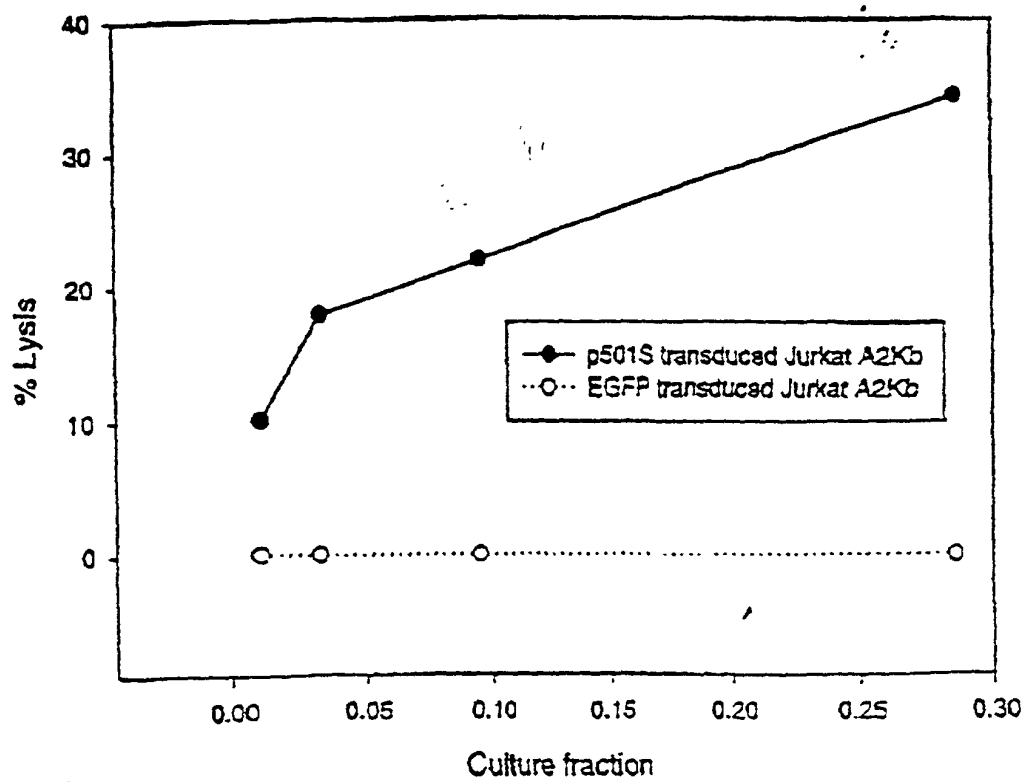


Figure 5

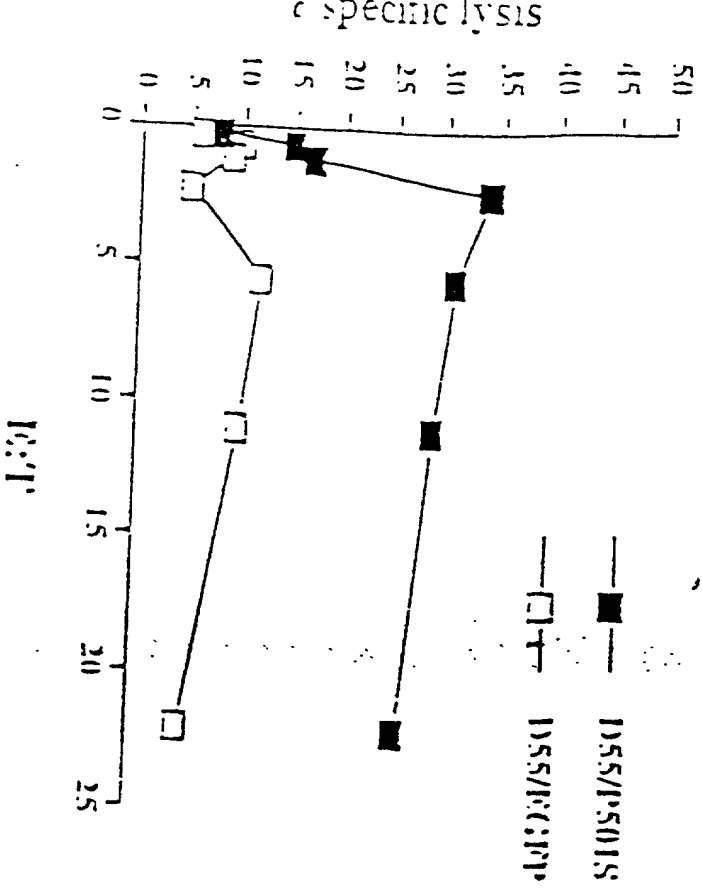


Fig. 6A

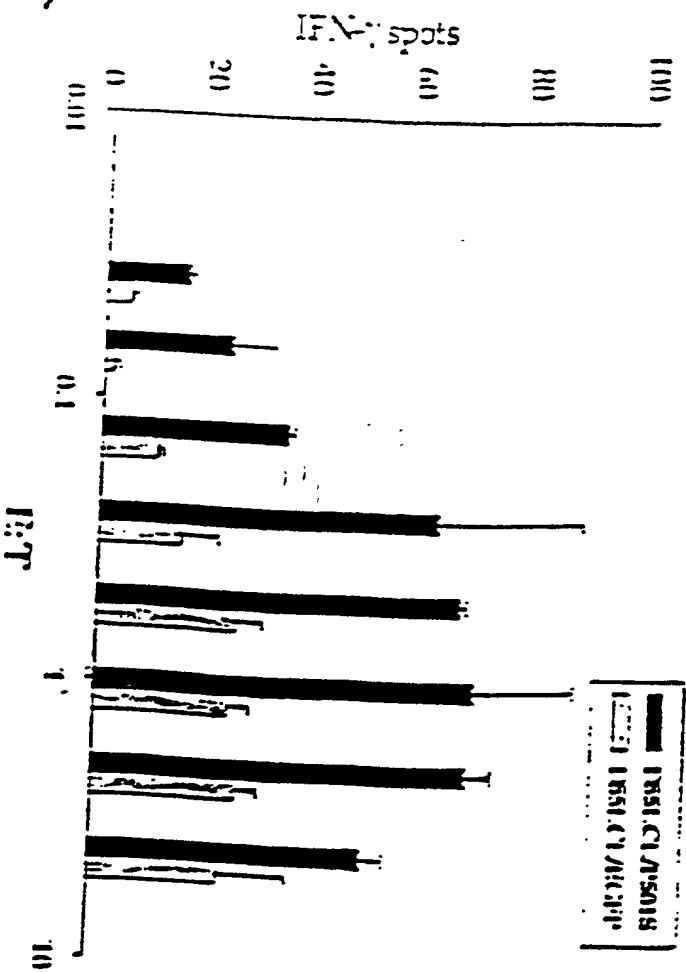
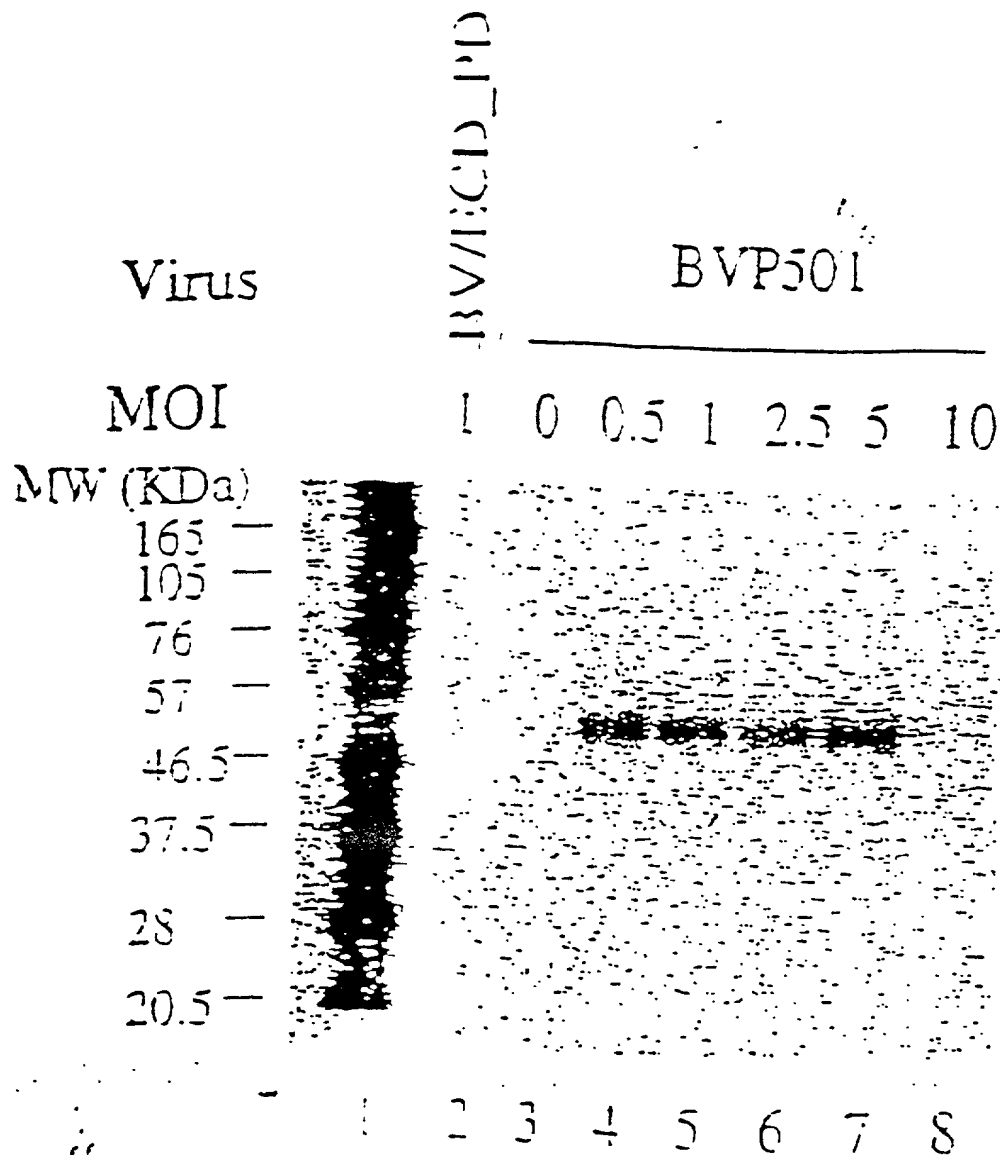


Fig. 6B

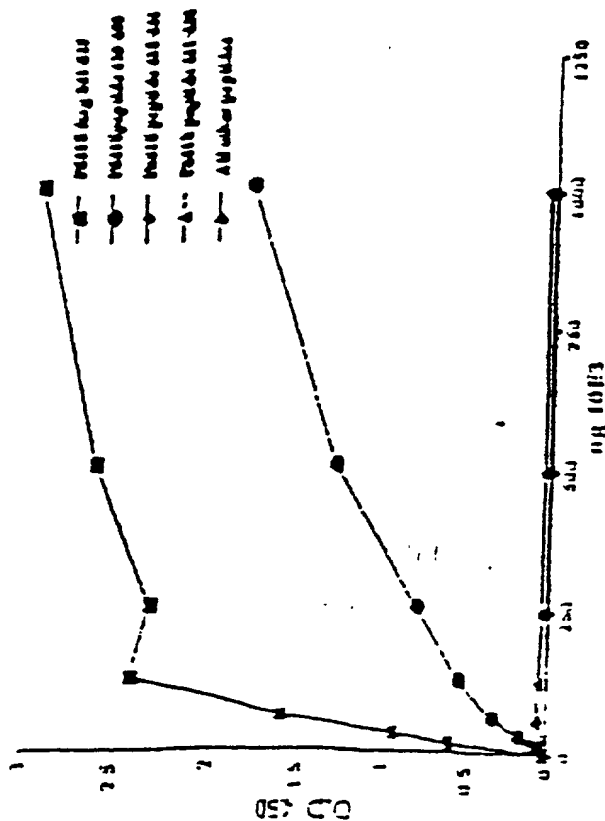
Expression of P501S by the Baculovirus Expression System



0.6 million high titer cell suspension in 6-well plate were infected with an unrelated control virus BV/ECD_PD (Lane 1, 3) or with recombinant baculovirus for P501S at different MOIs (Lane 4 - 8). Cell lysates were run on SDS-PAGE under the reducing condition and analyzed by Western blot with a monoclonal antibody against P501S (P501S-10E11-G4-D3). Lane 1 is the biotinylated protein molecular weight marker.

Fig 7

Figure 8. Mapping of the epitope recognized by 10E3-C4-D3



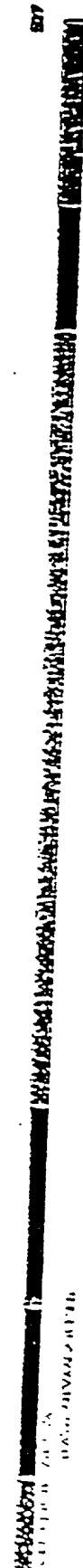
□ 10E3-C4-D3
● 10E3-C4-D3
△ 10E3-C4-D3
◇ 10E3-C4-D3
× All other peptides

Full length PSN18



PSN18 fragment used for immunization

II



PSN18 fragment used for immunization

PSN18 fragment used for immunization

PSN18 fragment used for immunization

PSN18 fragment used for immunization

PSN18 fragment used for immunization

PSN18 fragment used for immunization

PSN18 fragment used for immunization

7

Figure 1. Schematic of P501S with predicted transmembrane, cytoplasmic, and extracellular regions

AMVDRVAVSVLLRRK AQLALYNLTFTGLEVCLAAQT VVPRLLLENGVVEECFM TMVLGICRPVLIQLYCVPLLGSAK
 DIVVRCRYCHRRP FIVVALLSLGILLSLFLPRAGWL AGLLCTDPRPLF LALLILQVGLLDICQNVCPPL
 FALISDLERDPDHCRQ AYSVYAFMISLGGCTGYITPAI DVIDTSALAPVLCSTQNE
 CLPGLLEFLTCVAAATLY AEFVAGCPPEAEGLSAPVSPHCTPRARAFRMLGALLPRI
 DVLCCTNMPRTLR LPVAFLLCQWMAINFTTLYTTP VGEHELNYQGVPLAMPQTARHHYDEGVH
 NQSLQLFLQCAISLYPSLYM DRVQREFCTRAVYLAS VAAFPVAACIATCLSHSYAVVTA SAA
 LTGFTTSALQLPYTLASLY HREKQVFLPKYRGDTGCASSDSMTSELPGRKPGAPFNQHVQACQSGI
 LPPPPALCGASACDVSVYVYVCHPTFAVVPQRC LCLDLALLDSAPLLSQVAPSLF MGSIVQLSQS
 VTAYMYSAAGILGLVAIYPAT QVVFDKSDIAKYSK

Underlined sequence: Predicted transmembrane domain; Bold sequence: Predicted extracellular domain;
 Italic sequence: Predicted intracellular domain. Sequence in bold/underlined: used to generate polyclonal rabbit serum
 Localization of domains predicted using IMMTOPI (G.P. Tusnady and I. Simon (1998) Principles
 Governing Amino Acid Composition of Integral Membrane Proteins: Applications to topology Prediction. J. Mol. Biol. 287,
 489-506.

Fig. 9

Genomic Map of (5) Corlca Candidate Genes

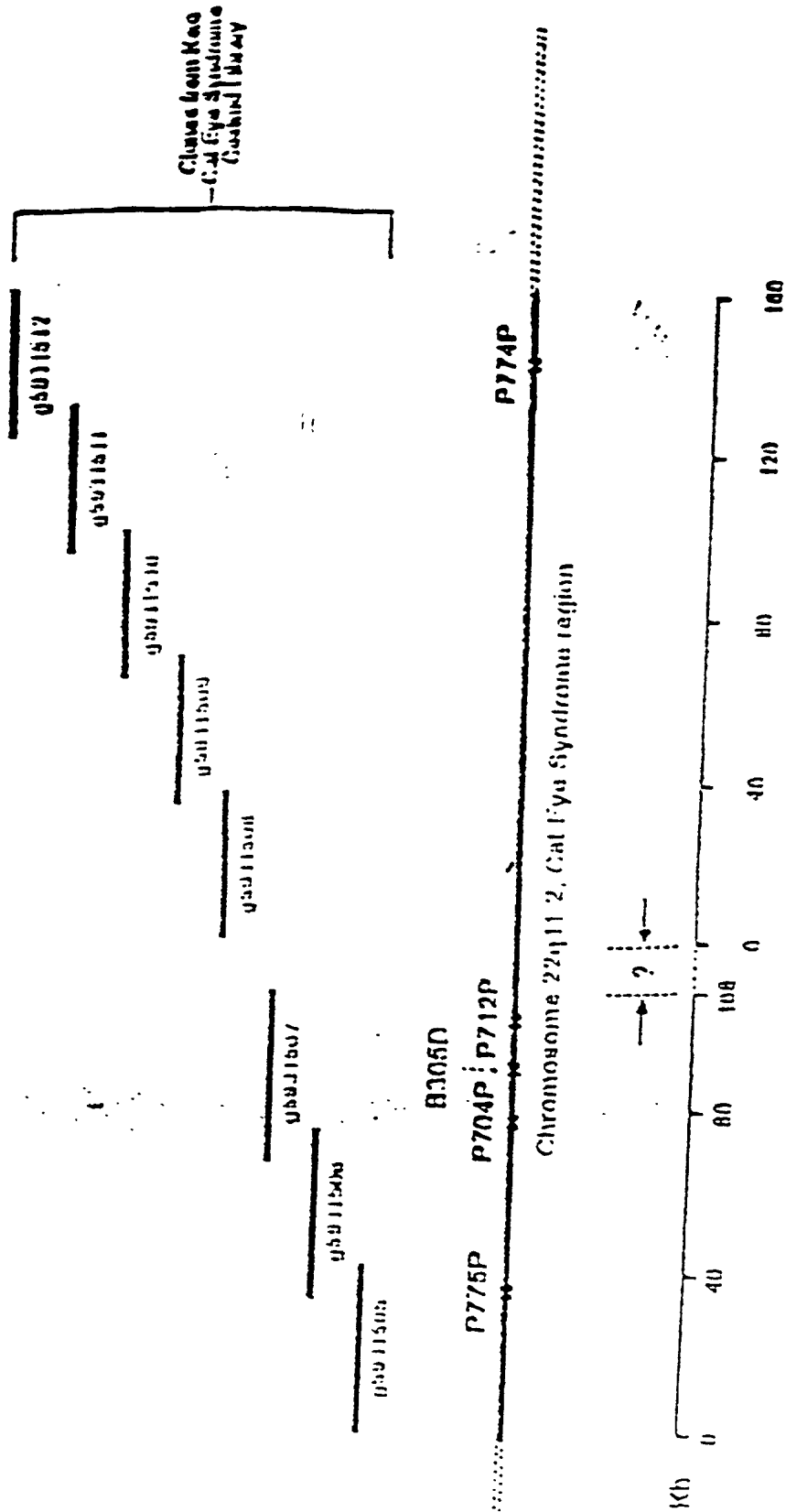
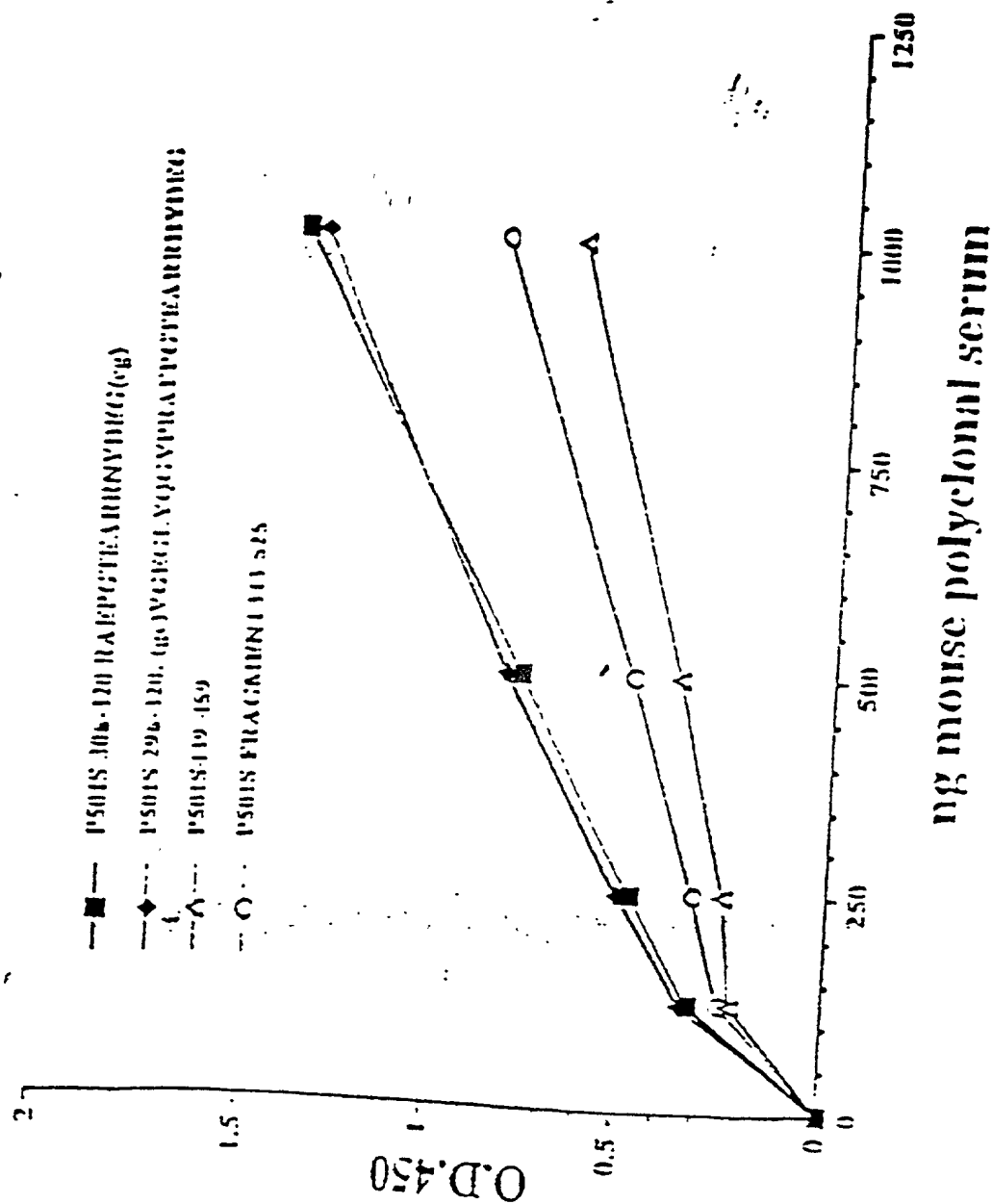


Fig. 10

FIGURE 4. Elisa assay of rabbit polyclonal antibody specificity



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360	370	380	390	400	410	420
.....						
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CACTGGCACCTGAAAACAACCAACCTGGTCAATTTCTGTGACCGGGGGGCGCCAAGAACTTCGCCCTGAAGC 490						
CGCGCATGCGCAAGATCTTCAAGCGGGCTCATCTACATCGCGCAGTCCAAAGGTGCTTGGATTCTCACGGG 560						
AGGCACCCATTATGGCTGACGAAAGTACATCGGGGAGGTGGTGAGAGATAACACTATCAGCAGGAGTTCA 630						
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.....						
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TTTCAACACAGTGAAGCAAGACAAAGGATAACTGAAATGGGC-GTGAAGTTCTGTGGAATGGAAATCAG 1330						
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1410	1420	1430	1440	1450	1460	1470
.....						
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1760	1770	1780	1790	1800	1810	1820
.....						
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Fig. 12A (i)

004590-053700

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3860	3870	3880	3890	3900	3910	3920
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VSNROT	LIRNCOAEGY	FLAQYLMDO	FTRDPLYLD	NNHTHLLV	DNGCHGHP	280
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LONKKELSK	VWECTRGCT	LAALGASK	LLKTLAK	VKNQINAAG	ESEELANEY	630
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710	720	730	740	750	760	770
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CDEVQWY	VNGVNYF	TDLWNVM	OTLGLFY	FIAGIV	FRHSENK	840
SRNLGPK	IIMLQRM	LIDVFF	FLFLFAY	WMVAF	3VARCGI	910
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NOCVWK	FCRYFLV	GEYCSR	LNIPFP	FIVFAY	FYMVKK	1050
1060	1070	1080	1090	1100	1110	1120
KENYLVK	INTKAND	TSEEMRR	FRQLDTK	LNCLK	ELLKEI	1096

Fig. 12B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Jiangchun Xu et al.
Filed : June 27, 2000
For : COMPOSITIONS AND METHODS FOR THERAPY AND
DIAGNOSIS OF PROSTATE CANCER

Docket No. : 210121.42716C16

Date : June 27, 2000

Box Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

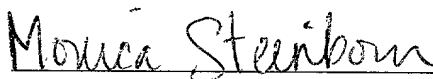
DECLARATION

Sir:

I, Monica Steinborn, in accordance with 37 C.F.R. § 1.821(f) do hereby declare that, to the best of my knowledge, the content of the paper entitled "Sequence Listing" and the computer readable copy contained within the floppy disk are the same.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated this 27th day of June, 2000.



Monica Steinborn
Legal Assistant

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Seattle, WA 98104-7092
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FAX (206) 682-6031

SEQUENCE LISTING

<110> Xu, Jiangchun
 Dillon, Davin C.
 Mitcham, Jennifer L.
 Harlocker, Susan L.
 Jiang, Yuqui
 Henderson, Robert A.
 Kalos, Michael D.
 Fanger, Gary R.
 Retter, Marc W.
 Stolk, John A.
 Day, Craig H.
 Vedvick, Thomas S.
 Carter, Darrick
 Li, Samuel
 Wang, Aijun
 Skeiky, Yasir A.W.
 Hepler, William

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 DIAGNOSIS OF PROSTATE CANCER

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<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(773)
<223> n = A,T,C or G

```

```

<400> 3
cttttgaaag aagggatggc tgggggtgttt aacagcagag gtgcagggcg ggggctcacg      60
tctgtctoct cactggtgat aaacgagccc cgttccttgt tgtgatcatg atgaacaacc      120
tctcaaaaag tcagaaccgg agtcacacag gcatctgtgc cgtcaaagat ttgacaccac      180
tctgccttcg tcttctttgc aaatacatct gcaaacttct tcttcatttc tggccaatca      240
tccatgctca tctgattggg aagtcatca gactttagtc canntccttt gatcagcagc      300
tcgtagaact ggggttctat tgctccaaca gccatgaatt ccccatctgc tgtcctgtaa      360
gtcgtataga aaggtgctcc accatccaac atgttctgtc ctcgaggggg ggcccgggtac      420

```

```

ccaattcgcc ctatantgag tegtattacg cgcgctcact ggccgctcgtt ttacaacgtc      480
gtgactggga aaaccttggg cgttaccaac ttaatcgctt tgcagcacat ccccttttcg      540
ccagctgggc gtaatancca aaaggccgcg accgatcgcc cttccaacag ttgcgcacct      600
gaatgggnaa atgggacccc cctgttacgg cgcattnaac ccccgcnngg tttngttggt      660
acccccacnt nnaccgctta cactttgccg gcgccttanc gcccgcctcc tttcnccttt      720
cttccttcc tttcncncn ctttcccccg ggggtttccc cntcaaacc cna                      773

```

```

<210> 4
<211> 828
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(828)
<223> n = A,T,C or G

```

```

<400> 4
cctcctgagt cctactgacc tgtgttttct ggtgtggagt ccagggctgc taggaaaagg      60
aatgggcaga cacagggtga tgccaatgtt tctgaaatgg gtataatttc gtcctctcct      120
tcggaacact ggctgtctct gaagacttct cgctcagttt cagtgaggac acacacaaag      180
acgtgggtga ccatgttggt tgtgggggtgc agagatggga ggggtggggc ccacctgga      240
agagtggaca gtgacacaag gtggacactc tctacagatc actgaggata agctggagcc      300
acaatgcatg aggcacacac acagcaagga tgacnctgta aacatagccc acgtgtcct      360
gngggcactg ggaagcctan atnaggccgt gagcanaaag aaggggagga tccactagtt      420
ctanagcggc cgccaccgcg gtgganctcc ancttttggt cccttttagtg agggttaatt      480
gcgcgcttgg cntaatcatg gtcatanctn tttcctgtgt gaaattgtta tccgctcaca      540
attccacaca acatacganc cggaaacata aantgtaaac ctgggggtgc taatgantga      600
ctaactcaca ttaattgcgt tgcgctcact gcccgccttc caatcnggaa acctgtcttg      660
ccncttgcct tnatgaatcn gccaaccccc ggggaaaagc gtttgcgttt tgggcgctct      720
tccgcttcct cnotcantta ntccctnenc tccgtcattc cggctgcngc aaaccggttc      780
accnctcca aaggggggtat tccggtttcc ccnaatccgg gganance                      828

```

```

<210> 5
<211> 834
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(834)
<223> n = A,T,C or G

```

```

<400> 5
tttttttttt tttttactga tagatggaat ttattaagct tttcacatgt gatagcacat      60
agttttaatt gcatccaaag tactaacaaa aactctagca atcaagaatg gcagcatggt      120
attttataac aatcaacacc tgtggctttt aaaatttggt tttcataaga taatttatac      180
tgaagtaaat ctagccatgc ttttaaaaaa tgcttttaggt cactccaagc ttggcagtta      240
acatttgcca taaacaataa taaaacaatc acaatttaat aaataacaaa tacaacattg      300
taggccataa tcatatacag tataaggaaa aggtggtagt gttgagtaag cagttattag      360
aatagaatac cttggcctct atgcaaatat gtctagacac tttgattcac tcagccctga      420

```


cattcagttt	tcaaagtagg	agacaggttc	tacagtatca	ttttacagtt	tccaacacat	480
tgaaaacaag	tagaaaatga	tgagttgatt	tttattaatg	cattacatcc	tcaagagtta	540
tcaccaaccc	ctcagttata	aaaaattttc	aagttatatt	agtcataata	cttggtgtgc	600
ttattttaaa	ttagtgtctaa	atggattaag	tgaagacaac	aatgggtccc	taatgtgatt	660
gatattggtc	atttttacca	gcttctaaat	ctnaactttc	aggcttttga	actggaacat	720
tgnatnacag	tgttccanag	ttncaaccta	ctggaacatt	acagtgtgct	tgattcaaaa	780
tgttattttg	ttaaaaatta	aattttaacc	tggtggaaaa	ataatttgaa	atna	834

<210> 6

<211> 818

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(818)

<223> n = A,T,C or G

<400> 6

tttttttttt	tttttttttt	aagaccctca	tcaatagatg	gagacataca	gaaatagtca	60
aaccacatct	acaaaatgcc	agtatcaggc	ggcggcttcg	aagccaaagt	gatgtttgga	120
tgtaaagtga	aatattagtt	ggcggatgaa	gcagatagtg	aggaaagtgt	agccaataat	180
gacgtgaagt	ccgtggaagc	ctgtggctac	aaaaaatgtt	gagccgtaga	tgccgtcggg	240
aatgggtgaag	ggagactcga	agtactctga	ggcttgtagg	agggtaaaat	agagaccag	300
taaaattgta	ataagcagtg	cttgaattat	ttggtttcgg	ttgttttcta	ttagactatg	360
gtgagctcag	gtgattgata	ctcctgatgc	gagtaatacg	gatgtgttta	ggagtgggac	420
ttctagggga	tttagcgggg	tgatgcctgt	tggggggccag	tgccctccta	gttgggggggt	480
aggggctagg	ctggagtggg	aaaaggctca	gaaaaatcct	gcgaagaaaa	aaacttctga	540
ggtaataaat	aggattatcc	cgtatcgaag	gccttttttg	acagggtggg	tgtggtggcc	600
ttggtatgtg	ctttctcggt	ttacatcgcg	ccatcattgg	tatatgggta	gtgtgttggg	660
ttantanggc	ctantatgaa	gaacttttgg	antggaatta	aatcaatngc	ttggccggaa	720
gtcattanga	nggctnaaaa	ggccctgtta	ngggctctgg	ctnggtttta	cccnacccat	780
ggaatncncc	ccccggacna	ntgnatccct	attcttaa			818

<210> 7

<211> 817

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(817)

<223> n = A,T,C or G

<400> 7

tttttttttt	tttttttttt	tggctctaga	gggggtagag	ggggtgctat	agggtaaata	60
cgggccctat	ttcaaagatt	tttaggggaa	ttaattctag	gacgatgggt	atgaaactgt	120
ggtttgctcc	acagatttca	gagcattgac	cgtagtatac	ccccggtcgt	gtagcgggtga	180
aagtggtttg	gttttagacgt	ccgggaattg	catctgtttt	taagcctaata	gtggggacag	240
ctcatgagtg	caagacgtct	tgtgatgtaa	ttattatacn	aatgggggct	tcaatcggga	300
gtactactcg	attgtcaacg	tcaaggagtc	gcaggctcgcc	tggttctagg	aataatgggg	360

gaagtatgta	ggaattgaag	attaatccgc	cgtagtcggt	gttctcctag	gttcaatacc	420
attggtggcc	aattgatttg	atggtaagg	gagggatcgt	tgaactcgtc	tgttatgtaa	480
aggatncctt	ngggatggga	aggcnatnaa	ggactangga	tnaatggcgg	gcangatatt	540
tcaaacngtc	tctanttcct	gaaacgtctg	aaatgttaat	aanaattaan	tttngttatt	600
gaatnttnng	gaaaagggct	tacaggacta	gaaaccaa	angaaaanta	atnntaangg	660
cnttatcntn	aaaggtmata	accnctccta	tnatcccacc	caatngnatt	ccccacncnn	720
acnattggat	nccccanttc	canaaanggc	cnccecccg	tgnannccnc	cttttgttcc	780
cttnantgan	ggttattcnc	ccctngcntt	atcancc			817

<210> 8

<211> 799

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (799)

<223> n = A,T,C or G

<400> 8

catttccggg	tttactttct	aaggaaagcc	gagcgggaagc	tgctaacgtg	ggaatcggtg	60
cataaggaga	actttctgct	ggcaogcgct	agggacaagc	gggagagcga	ctccgagcgt	120
ctgaagcgca	cgtcccagaa	ggtggacttg	gcaactgaaac	agctgggaca	catccgagag	180
tacgaacagc	gcctgaaagt	gctggagcgg	gaggtccagc	agtgtagccg	cgtcctgggg	240
tgggtggccg	angcctganc	cgtctctgct	tgctgcccc	angtgggccc	ccacccccctg	300
acctgcctgg	gtccaaacac	tgagccctgc	tggcggactt	caagganaac	ccccacangg	360
ggattttgct	cctanantaa	ggctcatctg	ggcctcggcc	ccccacactg	gttggccttg	420
tctttgangt	gagccccatg	tccatctggg	ccactgtcng	gaccaccttt	ngggagtgtt	480
ctccttacaa	ccacannatg	cccggtctct	cccggaaacc	antcccancc	tgngaaggat	540
caagnctgn	atccactnnt	netanaaccg	gcncncncg	cngtgggaacc	cnccttntgt	600
tccttttcnt	tnagggttaa	tnnccgcttg	gccttnccan	ngtcctncnc	nttttccnnt	660
gttnaaattg	ttangcnc	nccnntccn	cnnncnnan	cccgaaccnn	anntnnann	720
ncctgggggt	nccnncgat	tgaccnnc	nccctntant	tgcnttnggg	nncnntgccc	780
ctttccctct	nggganncg					799

<210> 9

<211> 801

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (801)

<223> n = A,T,C or G

<400> 9

acgccttgat	cctcccaggc	tgggactggt	tctgggagga	gccgggcatg	ctgtggtttg	60
taangatgac	actcccaaag	gtggctcctga	cagtggcca	gatggacatg	gggctcacct	120
caaggacaag	gccaccaggt	gcgggggccc	aagcccacat	gacccctact	ctatgagcaa	180
aatcccctgt	gggggcttct	ccttgaagtc	cgccancagg	gctcagtctt	tggacccang	240
caggtcatgg	ggttgtngnc	caactggggg	ccncaacgca	aaanggcnc	gggcctcngn	300

```

caccatcccc angacgcggc tacactnctg gacctccnc tccaccactt tcatgcgctg      360
ttcntaccgc cgnatntgtc ccanctgttt cngtgcenac tccancttct nggacgtgcg      420
ctacatacgc ccggantcnc nctcccgtt tgteccatc cagtnccan caacaaattt      480
cncctantg caccnattcc cacnttttnc agntttccnc nncgngcttc cttntaaaag      540
ggttgancccc cggaatatnc cccaaagggg gggggccngg tacccaactn cccctnata      600
gctgaantcc ccatnaccnn gnetcnatgg anccntcent tttaannacn ttctnaactt      660
gggaanancc ctgcncntn ccccnnttaa tccnccttg cnangnnct ccccnntcc      720
nccnnntng gcntntnann cnaaaaaggc ccmnnancaa tctcctnncn cctcanttgc      780
ccanccctcg aaatcgccn c

```

<210> 10

<211> 789

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(789)

<223> n = A,T,C or G

<400> 10

```

cagtctatnt ggccagtgtg gcagctttcc ctgtggctgc cggtgccaca tgccgtgtcc      60
acagtgtggc cgtggtgaca gcttcagcgc cctcaccgg gttcaccttc tcagccctgc      120
agatcctgcc ctacacactg gcctccctct accaccggga gaagcagggtg ttccctgcca      180
aataccgagg ggacactgga ggtgctagca gtgaggacag cctgatgacc agcttcctgc      240
caggccctaa gcctggagct ccttcccta atggacacgt ggggtgctgga ggcagtggcc      300
tgctcccacc tccaccgcgc ctctgcgggg cctctgcctg tgatgtctcc gtacgtgtgg      360
tggtgggtga gccaccgan gccagggtgg ttccgggccc gggcatctgc ctggacctgc      420
ccatcctgga tagtgcttcc tgctgtccca ngtggcccca tccctgttta tgggtccat      480
tgtccagctc agccagtctg tcaactgcta tatggtgtct gccgcaggcc tgggtctggg      540
cccatttact ttgtacaca ggtantattt gacaagaacg anttggccaa atactcagcg      600
ttaaaaaatt ccagcaacat tgggggtgga aggcctgcct cactgggtcc aactccccgc      660
tctgttaaac ccatggggc tgccggcttg gccgccatt tctgttgctg ccaaantnat      720
gtggctctct gctgccacct gttgctggct gaagtgcnta cngcncanct nggggggtng      780
ggngttccc

```

<210> 11

<211> 772

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(772)

<223> n = A,T,C or G

<400> 11

```

cccaccctac ccaaataatta gacaccaaca cagaaaagct agcaatggat tcccttctac      60
ttgtttaaata aaataagtta aatattttaa tgccgtgtgc tctgtgatgg caacagaagg      120
accaacaggc cacatcctga taaaaggtaa gaggggggtg gatcagcaaa aagacagtgc      180
tgtgggctga ggggacctgg ttcttgtgtg ttgcccctca ggactcttcc cctacaaata      240

```

```

actttcatat gttcaaatcc catggaggag tgtttcatcc tagaaactcc catgcaagag      300
ctacattaaa cgaagctgca ggtaagggg cttanagatg ggaaaccagg tgactgagtt      360
tattcagctc ccaaaaaccc ttctctaggt gtgtctcaac taggaggcta gctgttaacc      420
ctgagcctgg gtaatccacc tgcagagtc cgcattcca gtgcatggaa ccttctggc      480
ctccctgtat aagtccagac tgaaaccccc ttggaaggnc tccagtcagg cagccctana      540
aactggggaa aaaagaaaag gacgccccan cccccagctg tgcanctacg cacctcaaca      600
gcacagggtg gcagcaaaaa aaccacttta ctttggcaca aacaaaaact nggggggggca      660
accccggcac cccnangggg gttaacagga ancngggnaa cntggaaccc aattnaggca      720
ggccnccac cccnaatntt gctgggaaat ttttctccc ctaaattntt tc              772

```

<210> 12

<211> 751

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(751)

<223> n = A,T,C or G

<400> 12

```

gccccaatc cagctgccac accaccacg gtgactgcat tagttcggat gtcatacaaa      60
agctgattga agcaaccctc tactttttgg tcgtgagcct tttgcttggg gcaggtttca      120
ttggctgtgt tggtagcgtt gtcattgcaa cagaatgggg gaaaggcact gttctctttg      180
aagtanggtg agtcctcaaa atccgtatag ttggtgaagc cacagcactt gagccctttc      240
atgggtggtg tccacacttg agtgaagtct tectgggaac cataatcttt cttgatggca      300
ggcactacca gcaacgtcag ggaagtgtc agccattgtg gtgtacacca aggcgaccac      360
agcagctgcn acctcagcaa tgaagatgan gaggangatg aagaagaacg tcncgagggc      420
acacttgctc tcagtcttan caccatanca gcccntgaaa accaananca aagaccacna      480
cnccggctgc gatgaagaaa tnaccccneg ttgacaaact tgcatggcac tggganccac      540
agtggccna aaaatcttca aaaaggatgc cccatcnatt gaccccccaa atgccactg      600
ccaacagggg ctgccccacn cncnnaacga tgancnatt gnacaagatc tncntggtct      660
tnatnaacnt gaacctgcn tngtggctcc tgttcaggnc cnnngcctga cttctnaann      720
aangaactcn gaagncccca cngganannc g              751

```

<210> 13

<211> 729

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(729)

<223> n = A,T,C or G

<400> 13

```

gagccaggcg tccctctgcc tgcccactca gtggcaacac ccgggagctg ttttgcctt      60
tgtggancct cagcagtncc ctctttcaga actcantgcc aaganccctg aacaggagcc      120
accatgcagt gcttcagctt cattaagacc atgatgatcc tcttcaattt gctcatcttt      180
ctgtgtgggtg cagccctgtt ggcagtgggc atctgggtgt caatcgatgg ggcacccctt      240
ctgaagatct tcgggccact gtcgtccagt gccatgcagt ttgtcaacgt gggctacttc      300

```

```

ctcatcgag cccggtgtgt ggtcttagct ctaggtttcc tgggctgcta tgggtgctaag 360
actgagagca agtgtgccct cgtgacgttc ttcttcatcc tctctctcat cttcattgct 420
gagggtgcaa tgctgtgggc gccttggtgt acaccacaat ggctgagcac ttcttgacgt 480
tgctggtaat gcctgccatc aanaaaagat tatgggttcc caggaanact tcactcaagt 540
gttggaacac caccatgaaa gggctcaagt gctgtggctt cnnccaacta tacggatttt 600
gaagantcac ctacttcaaa gaaaanagtg cctttccccc atttctgttg caattgacaa 660
acgtcccaaa cacagccaat tgaaaacctg caccacaacc aaanggggtcc ccaaccanaa 720
attnaaggg

```

```

<210> 14
<211> 816
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(816)
<223> n = A,T,C or G

```

```

<400> 14
tgctcttcct caaagttggt cttgttgcca taacaaccac cataggtaaa gcgggcgag 60
tgctcgctga aggggttgta gtaccagcgc gggatgctct ccttgagag tctgtgtct 120
ggcaggtcca cgcagtgcc tttgtcactg gggaaatgga tgcgctggag ctctgcaaag 180
ccactcgtgt atttttcaca ggcagcctcg tccgacgcgt cggggcagtt ggggggtgtct 240
tcacactcca ggaaactgtc natgcagcag ccattgctgc agcggaactg ggtgggctga 300
cangtgccag agcacactgg atgggcgctt tccatgnnan gggccctgng ggaaagtccc 360
tgancccan anctgcctct caaangcccc acctgacaca ccccgacagg ctagaatgga 420
atcttcttcc cgaaaggtag ttnttcttgt tgcccaancc anccccntaa acaaactctt 480
gcanatctgc tccgnggggg tentantacc ancgtgggaa aagaaccca ggcngcgaa 540
caancttgtt tggatnccga gcnataatct nctnttctgc ttggtggaca gcaccantna 600
ctgtnnanct ttagncntg gtccctntgg gttgnncttg aacctaatn ccnntcaact 660
gggacaaggt aantngcct cctttnaatt cccnancntn cccctggtt tgggggtttt 720
cncnctccta cccagaaan nccgtgttcc cccccaacta ggggccnaaa ccnntnttc 780
cacaaccctn cccacccac gggttcngnt ggttng 816

```

```

<210> 15
<211> 783
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(783)
<223> n = A,T,C or G

```

```

<400> 15
ccaaggcctg ggcaggcata nacttgaagg tacaaccca ggaaccctg gtgctgaagg 60
atgtggaaaa cacagattgg cgcctactgc ggggtgacac ggatgtcagg gtagagagga 120
aagacccaaa ccaggtggaa ctgtggggac tcaaggaang cacctacctg ttccagctga 180
cagtgactag ctcagaccac ccagaggaca cggccaactg cacagtcact gtgctgtcca 240
ccaagcagac agaagactac tgcctcgcat ccaacaangt ggtcgcctgc cggggctctt 300

```

```

tcccacgctg gtactatgac cccacggagc agatctgcaa gagtttcggt tatggaggct 360
gcttgggcaa caagaacaac taccttcggg aagaagagtg cattctancc tgcnggggtg 420
tgcaagggtg gcctttgana ngcanctctg gggctcangc gactttcccc cagggccctt 480
ccatggaaaag gcgccatcca ntgttctctg gcacctgtca gcccacccag ttccgctgca 540
ncaatggctg ctgcacnac antttcctng aattgtgaca acacccccca ntgcccccaa 600
ccctcccaac aaagcttccc tgttnaaaaa tacnccantt ggcttttnac aaacnccgg 660
cncctccttt ttcccnntn aacaaagggc nctngccttt gaactgcccn aaccnaggaa 720
tctnccnngg aaaaantncc cccctgggtt cctnnaancc cctccncaa anctncccc 780
ccc 783

```

```

<210> 16
<211> 801
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1) ... (801)
<223> n = A,T,C or G

```

```

<400> 16
gccccaatc cagctgccac accacccacg gtgactgcat tagttcggat gtcatacaaaa 60
agctgattga agcaaccctc tacttttttg tctgtagcct tttgcttggg gcaggtttca 120
ttggctgtgt tgggtgacgtt gtcattgcaa cagaatgggg gaaaggcact gttctctttg 180
aagtaggggtg agtcctcaaa atccgtatag ttgggtgaagc cacagcactt gagccctttc 240
atggtggtgt tccacacttg agtgaagtct tcctgggaac cataatcttt cttgatggca 300
ggcactacca gcaacgtcag gaagtgtcga gccattgtgg tgtacaccaa ggcgaccaca 360
gcagctgcaa cctcagcaat gaagatgagg aggaggatga agaagaacgt cncgagggca 420
cacttgctct ccgtcttagc accatagcag cccangaaac caagagcaaa gaccacaacg 480
ccngctgcga atgaaagaaa ntacccacgt tgacaaactg catggccact ggacgacagt 540
tggcccgaa atcttcagaa aagggatgcc ccacgattg aacacccana tgccactgc 600
cnacagggct gcnccnncn gaaagaatga gccattgaag aaggatcntc ntggctcttaa 660
tgaactgaaa cctgcatgg tggccctgt tccaggctct tggcagtga ttctganaaa 720
aaggaacngc ntnagcccc ccaaangana aaacaccccc ggggtgttgc ctgaattggc 780
ggccaaggan cctgccccn g 801

```

```

<210> 17
<211> 740
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1) ... (740)
<223> n = A,T,C or G

```

```

<400> 17
gtgagagcca ggcgtccctc tgcctgccca ctgagtggca acacccggga gctgttttgt 60
cctttgtgga gcctcagcag ttccctcttt cagaactcac tgccaagagc cctgaacagg 120
agccaccatg cagtgttca gcttcattaa gaccatgatg atcctcttca atttgctcat 180
ctttctgtgt ggtgcagccc tgttggcagt gggcatctgg gtgtcaatcg atggggcatc 240

```

```

ctttctgaag atcttcgggc cactgtcgtc cagtgccatg cagtttgtca acgtgggcta      300
cttcctcatc gcagccggcg ttgtggtctt tgcctcttgggt ttectgggct gctatgggtgc      360
taagacggag agcaagtgtg ccctcgtgac gttctctctc atcctcctcc tcctcttcat      420
tgctgaagtt gcagctgctg tggtcgcctt ggtgtacacc acaatggctg aaccattcct      480
gacgttgctg gtantgcctg ccatcaanaa agattatggg tcccaggaa aaattcactc      540
aantntggaa caccnccatg aaaagggctc caatttctgn tggcttcccc aactataccg      600
gaattttgaa agantcncct tacttccaaa aaaaaanant tgccttttnc cccnttctgt      660
tgcaatgaaa acntcccaan acngccaatn aaaacctgcc cnnncaaaaa ggntcncaaa      720
caaaaaaant nnaaggggtn

```

```

<210> 18
<211> 802
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(802)
<223> n = A,T,C or G

```

```

<400> 18
ccgctgggtg cgctgggtcca gngnagccac gaagcacgtc agcatacaca gcctcaatca      60
caaggtcttc cagctgccgc acattacgca gggcaagagc ctccagcaac actgcatatg      120
ggatacactt tacttttagca gccaggggtga caactgagag gtgtcgaagc ttattcttct      180
gagcctctgt tagtggagga agattccggg cttcagctaa gtagtcagcg tatgtcccat      240
aagcaaacac tgtgagcagc cggaaggtag aggcaaagtc actctcagcc agctctctaa      300
cattggggcat gtccagcagt tctccaaaca cgtagacacc agnggcctcc agcacctgat      360
ggatgagtgt ggccagcgct gcccccttgg ccgacttggc taggagcaga aattgctcct      420
ggttctgccc tgtcaccttc acttccgcac tcactactgc actgagtgtg ggggacttgg      480
gctcaggatg tccagagacg tggttccgcc cctcnctta atgacaccgn ccanncaacc      540
gtcggctccc gccgantgng ttcgctgtnc ctgggtcagg gtctgctggc cnetacttgc      600
aancttcgtc nggcccattg aattcaccnc accggaactn gtangatcca ctntttctat      660
aaccggnctc caccgcnntt ggaactccac tcttnttnc tttacttgag ggtaaggctc      720
acccttncg ttaccttggt ccaaaccntn centgtgtcg anatngtnaa tcnggncna      780
tnccancnc atangaagcc ng

```

```

<210> 19
<211> 731
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(731)
<223> n = A,T,C or G

```

```

<400> 19
cnaagcttcc aggtnacggg ccgcnaancc tgaccnagg tancanaang cagnctgcgg      60
gagccaccg tcacngngng gngtctttat nggagggggc ggagccacat cnetggacnt      120
cntgacccca actccccnc nncantgca gtgatgagtg cagaactgaa ggtnacgtgg      180
caggaaccaa gancaaannc tgctccnntc caagtcggcn nagggggcgg ggctggccac      240

```

```

gencatccnt cnagtgtctgn aaagccccnn cctgtctact tgtttggaga acngcnnnga      300
catgcccagn gttanataac nggcngagag tnantttgcc tctcccttcc ggctgcgcan      360
cngntntgct tagnggacat aacctgacta cttaactgaa cccnngaate tncnccccct      420
ccactaagct cagaacaaaa aacttcgaca ccactcantt gtcacctgnc tgctcaagta      480
aagtgtaccc catncccaat gtntgtctnga ngctctgncc tgcnttangt tcgggtcctgg      540
gaagacctat caattnaagc tatgtttctg actgcctctt gctccctgna acaancnacc      600
cnncnntcca aggggggggnc ggcccccaat ccccccaacc ntnaattnan tttanccccc      660
ccccnnggcc cggcctttta cnancntcnn nnacngggna aaaccnnngc tttncccaac      720
nnaatccncc t

```

```

<210> 20
<211> 754
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(754)
<223> n = A,T,C or G

```

```

<400> 20
tttttttttt tttttttttt taaaaacccc ctccattnaa tgnaaacttc cgaaattgtc      60
caacccctc ntccaaatnn cnttttcgg gnggggggttc caaacccaan ttanntttgg      120
annttaaatt aaatnttntt tggnggnnna anccnaatgt nangaaagtt naaccanta      180
tnancctnaa tncctggaaa cngtngntt ccaaaaatnt ttaaccctta antcctccg      240
aaatngttna nggaaaaccc aanttctcnt aagggtgttt gaaggntnaa tnaaaanccc      300
nnccaattgt ttttngccac gcctgaatta attggnntcc gntgttttcc nttaaaanaa      360
ggnnancccc gggtantnaa tccccccnnc cccaattata ccganttttt ttngaattgg      420
ganccncgg gaattaacgg ggnnnnntccc tnttgggggg cnggnncccc cccntcggg      480
ggttngggnc aggnccnaat tgtttaaggg tccgaaaaat ccctccnaga aaaaaanctc      540
ccagnttgag nntnggggtt nccccccccc cangggccct ctcgnanagt tgggggtttg      600
ggggcctggg attttntttc ccctnttnc tccccccccc ccnggganag aggttngngt      660
ttgtntcnnn ggccccnccn aaganccttn ccganttnan ttaaatecnt gcctnggcga      720
agtcctntgn agggntaaan ggccccctnn cggg

```

```

<210> 21
<211> 755
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(755)
<223> n = A,T,C or G

```

```

<400> 21
atcancccat gaccccnac nngggaccnc tcancgggnc nnncnaccnc cggccnatca      60
nngtnagnnc actncnnttn natcacnccc cncnactac gccncnanc cnacgcncta      120
nncanatncc actganngcg cgangtngan ngagaaanct nataccanag ncaccanacn      180
ccagctgtcc nanaangcct nnnatacngg nnnateccaat ntgnancctc cnaagtattn      240
nncnncanat gattttcctn anccgattac ccntncccc tanccctcc cccccaacna      300

```



```

ctnccnacc  tacntcttcn  nagctgtcnn  acccctngtn  cgnaccccc  naggtcggga  300
tcgggttttn  nntgaccgng  cnnccctcc  cccctccat  nacgancnc  ccgcaccacc  360
nanngcncgc  nccccgnct  cttegcnc  ctgtctntn  cccctgtngc  ctggcncngn  420
accgcattga  ccctcgccnn  ctncnngaaa  ncgnanacgt  ccgggttggn  annancgctg  480
tgggnnngcg  tctgncgcgc  gtctcttcn  ncncttcca  ccctcttct  tacngggctc  540
ccncccttc  tcnnncacnc  cctgggacgc  tntctntgc  ccccttnac  tcccccttc  600
cgcgtgnc  cgnccccc  ntcatttnca  nacgntcttc  acaannncct  ggntnntcc  660
cnancngnc  gtcancnag  ggaagggngg  ggnncnntg  nttgacgttg  ngngangtc  720
cgaanantcc  tcncntcan  cncctaccct  cgggcgnct  ctngttnc  aacttancaa  780
ntctcccccg  ngngcncnt  tcagctcnc  cccccnct  ctctgcantg  tntctgctc  840
tnaccnntac  gantnttcgn  cncctcttt  cc  872

```

<210> 24

<211> 815

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(815)

<223> n = A,T,C or G

<400> 24

```

gcatgcaagc  ttgagtattc  tatagngtca  cctaaatanc  ttggcntaat  catggtcnta  60
nctgncttcc  tgtgtcaa  gtatacnaa  tanatatgaa  tctnatntga  caaganngta  120
tcntncatta  gtaacaantg  tnntgtccat  cctgtengan  canattccca  tnnattncgn  180
cgcattcn  gncantatn  taatngggaa  ncnntnnn  ncacnncat  ctatcntncc  240
gncctgac  tggagagat  ggatnanttc  tnntntgacc  nacatgttca  tcttggattn  300
aanancccc  cgcngnccac  cggttngng  cnagcncnt  ccaagacctc  ctgtggaggt  360
aacctgcgtc  aganncatca  aacntgggaa  accgcncnc  angtnnaagt  ngnnncanan  420
gatcccgctc  aggnntnacc  atcccttcnc  agcgcacct  ttngtgcctt  anagnnagc  480
gtgtccnanc  cnccaacat  ganaocgcgc  agnccanccg  caattnggca  caatgtcgnc  540
gaaccccta  gggggganna  tncaaanccc  caggattgtc  cncncangaa  atccncanc  600
ccnccctac  ccncttttg  gacngtgacc  aantcccgga  gtncagtc  ggcngnctc  660
ccccaccgt  nncntgggg  ggggtgaant  cngnntcanc  cngncgaggn  ntcgnaagga  720
accgncctn  ggcgaanng  ancnntcnga  agncncnt  cgtataacce  cccctcncca  780
nccnancgnt  agntcccccc  cngggtnccg  aangg  815

```

<210> 25

<211> 775

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(775)

<223> n = A,T,C or G

<400> 25

```

ccgagatgtc  tcgtccgtg  gccttagctg  tgctcgct  actctctctt  tctggcctgg  60
aggctatcca  gcgtactcca  aagattcagg  tttactcacg  tcatccagca  gagaatggaa  120

```

```

agtcaaattt cctgaattgc tatgtgtctg ggtttcatcc atccgacatt gaanttgtact 180
tactgaagaa tgganagaga attgaaaaag tggagcattc agacttgtct ttcagcaagg 240
actggctctt ctatctcntg tactacactg aattcacccc cactgaaaaa gatgagtatg 300
cctgccgtgt gaaccatgtg actttgtcac agcccaagat agttaagtgg gatcgagaca 360
tgtaagcagn cnnecatggaa gtttgaagat gccgcatttg gattggatga attccaaatt 420
ctgcttgctt gcnttttaat antgatatgc ntatacacc taccctttat gnccccaaatt 480
tgtaggggtt acatnantgt tcnctnngga catgatcttc ctttataant ccncnttcg 540
aattgccgt cncncngtn ngaatgtttc cnaaaccacg gttggctccc ccaggtcncc 600
tcttacggaa gggcctgggc cnccttncaa ggttggggga accnaaaatt tcncttntgc 660
ccnccncca cnntcttng nncncanttt ggaacccttc cnattcccct tggcctcnna 720
nccttnncta anaaaacttn aaancgtngc naaanntttt acttcccccc ttacc 775

```

<210> 26

<211> 820

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(820)

<223> n = A,T,C or G

<400> 26

```

anattantac agtgtaatct tttcccagag gtgtgtanag ggaacggggc ctagaggcat 60
cccanagata ncttatanca acagtgtctt gaccaagagc tgctgggcac atttcctgca 120
gaaaagggtg cgggtcccat cactcctcct ctcccatagc catcccagag gggtgagtag 180
ccatcangcc ttcggtggga gggagtcang gaaacaacan accacagagc anacagacca 240
ntgatgacca tgggcgggag cgagcctctt ccctgnaccg gggtggcana nganagccta 300
nctgaggggt cacactataa acgttaacga ccnagatnan cacctgttc aagtgcaccc 360
ttcctacctg acnaccagn accnnnaact gngcctggg gacagcnctg ggancagcta 420
acnnagcact cacctgcccc cccatggcgg tncgntccc tggctcctgnc aagggaagct 480
ccctgttgga attncgggga naccaaggga nccccctcct ccantgtga aggaaaaann 540
gatggaattt tnccttccg gccnntcccc tcttcttta cagccccct nntactctc 600
tccctctntt ntctgncnc acttttnacc ccnnnatttc ccttnattga tcggannctn 660
ganattccac tnnegcctnc cntcnatcng naanacnaaa nactntctna ccnnggggat 720
gggnncctcg ntcctcctct ctttttctct accncnntt ctttgctct ccttngatca
780tccaaccntc gntggccntn ccccccnnn tcttttncce 820

```

<210> 27

<211> 818

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(818)

<223> n = A,T,C or G

<400> 27

```

tctgggtgat ggctcttcc tctcagggga cctctgactg ctctgggcca aagaatctct 60
tgtttcttct ccgagcccca ggcagcgggtg attcagccct gcccaacctg attctgatga 120

```

```

ctgcggatgc tgtgacggac ccaaggggca aataggggtcc caggggtccag ggagggggcgc      180
ctgctgagca cttccgcccc tcacctgcc cagccctgc catgagctct gggctgggtc      240
tccgcctcca gggttctgct cttccangca ngccancaag tggcgctggg ccacactggc      300
ttcttctgct ccntccctg gctctgante tctgtcttcc tgcctgtgc angcnccttg      360
gatctcagtt tccctcnctc anngaactct gtttctgann tcttcantta actntgantt      420
tatnaccnan tggnetgtnc tgtcnnaact taatgggccc gaccggctaa tccctccctc      480
nctcccttcc anttcnnna accngettnc cntctctcc cntancccg ccngggaanc      540
ctcctttgcc ctnaccangg gccnnnaccg cccntnnctn ggggggcng gttnctncnc      600
ctgntnnccc cncctcnnt tncctcgcc cnnncnccg nngcannttc ncngtcccn      660
tnnctcttcn ngntcgnaa ngntcnctn tnnnnngncc ngntnntncc tccctctcnc      720
cnnntgnang tnnntnnnc ncngncccc nnnnnnnnn nggnntnnn tctnccngc      780
cccnccccc ngnattaagg cctccnctc cgggcnc      818

```

```

<210> 28
<211> 731
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(731)
<223> n = A,T,C or G

```

```

<400> 28
aggaagggcg gagggatatt gtangggatt gagggatagg agnataangg gggaggtgtg      60
tcccaacatg anggtgnngt tctcttttga angaggggtg ngtttttann ccnggtgggt      120
gattnaaccc cattgtatgg agnnaaagg tttnagggat ttttcggctc ttatcagtat      180
ntanattcct gtnaatcgga aaatnatntt tcnnccggaa aatnttgctc ccatccgnaa      240
attnctcccg ggtagtgc tntngggggg cngccangtt tcccaggctg ctanaatcgt      300
actaaagntt naagtgggan tncaaataa aacctnncac agagnatccn tacccgactg      360
tnmnttncct tcgccctntg actctgcng agcccaatac ccnngngnat gtcncccn      420
nnngcgcnc tgaaannnnc tcngggetnn gancatcang gggtttcgca tcaaagcnn      480
cgtttncat naaggcactt tngcctcct caaccnctng ccctcncca tttngccgtc      540
nggttncct acgctnntng cncctnnntn ganattttnc ccgcctnggg naancctcct      600
gnaatgggta gggncctntc ttttnaccnn gnggtntact aatcnctnc acgctnctt      660
tctnaccccc ccccttttt caatcccanc ggcnaatggg gtctccccnn cgangggggg      720
nnnccannc c

```

```

<210> 29
<211> 822
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(822)
<223> n = A,T,C or G

```

```

<400> 29
actagtccag tgtggtggaa ttccattgtg ttggggncnc ttctatgant antnttagat      60
cgctcanacc tcacancctc ccnacnangc ctataangaa nannaataga nctgtncntt      120

```

```
<210> 30
<211> 787
<212> DNA
<213> Homo sapien
```

```
<220>
<221> misc_feature
<222> (1)...(787)
<223> n = A,T,C or G
```

```
<210> 31
<211> 799
<212> DNA
<213> Homo sapien
```

```
<220>
<221> misc_feature
<222> (1) ... (799)
<223> n = A,T,C or G
```

<400> 31
 tttttttttt tttttttggc gatgctactg tttaattgca ggaggtgggg gtgtgtgtac 60

```

catgtaccag ggctattaga agcaagaagg aaggagggag ggcagagcgc cctgctgagc 120
aacaaaggac tcctgcagcc ttctctgtct gtctcttggc gcaggcacat ggggaggcct 180
cccgagggtt gggggccacc agtccagggg tgggagcact acanggggtg ggagtgggtg 240
gtggctggtn cnaatggcct gncacanatc cctacgattc ttgacacctg gatttcacca 300
ggggaccttc tgttctccca nggnaacttc nttnatctcn aaagaacaca actgtttctt 360
cngcanttct ggctgttcat ggaaagcaca ggtgtccnat ttnggctggg acttgggtaca 420
tatggttccg gccacactct ccntcnaaen aagtaattca ccccccccn ccntctnttg 480
cctggggcct taantacca caccggaact canttantta ttcattctng gntgggcttg 540
ntnatcnccn cctgaangcg ccaagttgaa aggccacgcc gtncccnctc cccatagnan 600
nttttnncnt canctaagtc cccccnggc aacnatccaa tcccccccn tggggggccc 660
agcccanggc ccccgntctg ggnnnccngn cncgnantec ccaggntctc ccantcngnc 720
ccnnngcncc cccgcacgca gaacanaagg ntngagccnc cgcannnnnn nggttnncac 780
ctgcccccc ccnncgngg

```

<210> 32

<211> 789

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(789)

<223> n = A,T,C or G

<400> 32

```

tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 60
ttttnccnag ggcaggttta ttgacaacct cncgggacac aancaggctg gggacaggac 120
ggcaacaggc tccggcggcg gcggcggcg ccctacctgc ggtaccaaen ntgcagcctc 180
cgctcccgtt tgatnttctt ctgcagctgc aggatgcctt aaaacagggc ctcgcccntn 240
ggtgggcacc ctgggatttn aatttccacg ggcacaatgc ggtcgcancc cctcaccacc 300
nattaggaat agtggnttta ccnccnccg ttggcncact ccccntggaa accacttntc 360
gcggtctcgg catctggtct taaaccttgc aaacnctggg gccctctttt tggttantnt 420
nccngccaca atcatnactc agactggcnc gggctggccc caaaaaancn ccccaaaacc 480
ggncatgtc ttncgggggt tgcctgcnatn tncatcacct cccgggcnca ncaggncaac 540
ccaaaagttc ttgnggcccn caaaaaancn cccgggggnc ccagtttcaa caaagtcac 600
ccccttggcc cccaaatcct ccccccgntt nctgggtttt ggaacccacg cctctnnctt 660
tggnnggcaa gntggntccc ccttcgggcc ccgggtgggc ccnctctaa ngaaaacncc 720
ntcctnnnca ccatcccccc nngnnacgnc tancaangna tccctttttt tanaaacggg 780
ccccccnccg

```

<210> 33

<211> 793

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(793)

<223> n = A,T,C or G

<400> 33

```

gacagaacat gttggatggt ggagcacctt tctatacgac ttacaggaca gcagatgggg      60
aattcatggc tgttggagca atanaacccc agttctacga gctgctgac aaaggacttg      120
gactaaagtc tgatgaactt cccaatcaga tgagcatgga tgattggcca gaaatgaana      180
agaagtttgc agatgtatth gcaaagaaga cgaaggcaga gtggtgtcaa atctttgacg      240
gcacagatgc ctgtgtgact cgggttctga cttttgagga ggttggtcat catgatcaca      300
acaangaacg gggctcgttt atcaccantg aggagcagga cgtgagcccc cgccctgcac      360
ctctgctgtt aaacacccca gccatccctt ctttcaaaag ggatccacta cttctagagc      420
ggncgccacc gcggtggagc tccagctttt gttcccttta gtgagggtta attgcgcgct      480
tggcgtaatc atggtcatan ctgtttcctg tgtgaaattg ttatccgctc acaattccac      540
acaacatacg anccggaagc atnaaatttt aaagcctggg ggtngcctaa tgantgaact      600
nactcacatt aattggcttt gcgctcaactg cccgctttcc agtccggaaa acctgtcctt      660
gccagctgcc nttaatgaat cnggccaccc cccggggaaa aggcngtttg cttnttgggg      720
cgcncctccc gctttctcgc ttctgaant ccttcccccc ggtctttcgg cttgcggcna      780
acggtatcna cct                                     793

```

```

<210> 34
<211> 756
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(756)
<223> n = A,T,C or G

```

```

<400> 34
gccgcgaccg gcatgtacga gcaactcaag ggcgagtgga accgtaaaag ccccaatctt      60
ancaagtgcg gggaanagct gggtcgactc aagctagtth ttctggagct caacttcttg      120
ccaaccacag ggaccaagct gaccaaacag cagctaattc tggcccgtga catactggag      180
atcggggccc aatggagcat cctacgcaan gacatcccct ctttcgagcg ctacatggcc      240
cagctcaaat gctactactt tgattacaan gagcagctcc ccgagtcagc ctatatgcac      300
cagctcttgg gcctcaacct cctcttcctg ctgtcccaga accgggtggc tgantnccac      360
acgganttgg ancggctgcc tgcccanga catacanacc aatgtctaca tcnaccacca      420
gtgtcctgga gcaatactga tgganggcag ctaccncaaa gtnttcctgg ccnagggtaa      480
catccccgcg cgagagctac accttcttca ttgacatcct gctcgacact atcagggatg      540
aaaatcgcn ggttgctcca gaaaggctnc aanaanatcc ttttcnctga aggcctcccg      600
atncnctagt nctagaatcg gcccgccatc gcggtgganc ctccaacctt tcgttnccct      660
ttactgaggg ttnattgccg cccttggcgt tatcatggtc acnccngttn cctgtgttga      720
aatnttaac cccccacaat tccacgcna cattnng                                     756

```

```

<210> 35
<211> 834
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(834)
<223> n = A,T,C or G

```

```

<400> 35

```

```

ggggatctct anatchnacct gnatgcatgg ttgtcgggtgt ggtecgctgtc gatgaanatg      60
aacaggatct tgccttgaa gctctcggtc gctgtnttta agttgctcag tctgccgtca      120
tagtcagaca cncctctggg caaaaaacan caggatntga gtcttgattt cacctccaat      180
aatcttcnng gctgtctgct cggatgaactc gatgacnang ggcagctggg tgtgtntgat      240
aaantccanc angttctcct tggatgacctc cctttcaaag ttgttcgggc cttcatcaaa      300
cttctnnaan angannancc canctttgtc gagctggnat ttgganaaca cgtcactgtt      360
ggaaactgat cccaaatggg atgtcatcca tgcctctgtc tgcctgcaaa aaacttgctt      420
ggcncaaadc cgactcccn tcttgaaag aagccnatca cccccctc cctggactcc      480
nncaangact ctncgctnc cccntccnng cagggttggg ggcannccgg gcccntgcgc      540
ttcttcagcc agttcacnat ntcatcagc cctctgcca gctgtntat tcttggggg      600
ggaanccgtc tctcccttcc tgaannaact ttgaccgtng gaatagccgc gcntcncnt      660
acntnctggg ccgggttcaa antccctccn ttgncnntcn cctcgggcca ttctggattt      720
nccnaacttt tctcttcccc cncccnccgg ngtttgntt tttcatnggg ccccaactct      780
gctnttggcc antccctggg gggcntntan cnccccctnt ggtcccntng ggcc      834

```

<210> 36

<211> 814

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(814)

<223> n = A,T,C or G

<400> 36

```

cggncgcttt ccngccgcgc cccgtttcca tgacnaaggc tcccttcang ttaaatacnn      60
cctagnaacc attaatgggt tgctctacta atacatcata cnaaccagta agcctgcca      120
naacgccaac tcaggccatt cctaccaaag gaagaaaggc tggctctctcc accccctgta      180
ggaaaggcct gccttgtaag acaccacaat nccgctgaat ctnaagtctt gtgttttact      240
aatggaaaaa aaaaataaac aanagggtttt gttctcatgg ctgccaccg cagcctggca      300
ctaaaacanc ccagcgctca cttctgcttg ganaaatatt ctttgctctt ttggacatca      360
ggcttgatgg tatcactgcc acntttccac ccagctgggc ncccttcccc catntttgtc      420
antganctgg aaggcctgaa ncttagtctc caaaagtctc ngcccacaag accggccacc      480
aggggangtc ntttncagtg gatctgcaa anantaccn tatcatcnnt gaataaaaag      540
gcccctgaac ganatgcttc cancanctt taagacccat aatcctngaa ccatggtgcc      600
cttccggtct gatccnaaag gaatgttcc gggcccant cctcctttg ttntttacgt      660
tgtnttgga cctgctngn atnaccnaan tganatcccc ngaagcacc tnccttggc      720
atttganttt cntaaattct ctgccctacn nctgaaagca cnattccctn ggcnccnaan      780
ggngaactca agaaggctcn ngaaaaacca cncn      814

```

<210> 37

<211> 760

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(760)

<223> n = A,T,C or G

<400> 37

```

gcatgctgct cttcctcaaa gttgttcttg ttgccataac aaccaccata ggtaaagcgg      60
gcgcagtggt cgctgaagggt gttgtagtac cagcgcgaggga tgctctcctt gcagagtcct    120
gtgtctggca ggtccacgca atgccctttg tcaactgggga aatggatgcg ctggagctcg      180
tcnaanccac tcgtgtattt ttcacangca gcctcctcgg aagcntccgg gcagttgggg      240
gtgtcgtcac actccactaa actgtcgatn cancagccca ttgctgcagc ggaactgggt      300
gggctgacag gtgccagaac aacttgatn ggcctttcca tggaaggggc tgggggaaat      360
cncctnancc caaactgcct ctcaaaggcc accttgacac ccccgacagg ctagaaatgc      420
actcttcttc ccaaaggtag ttgttcttgt tgcccaagca ncctccanca aacccaaanc      480
ttgcaaaatc tgctccgtgg gggtcatnnn taccanggtt ggggaaanaa acccggcngn      540
ganccncctt gtttgaatgc naaggnaata atcctcctgt cttgcttggg tggaanagca      600
caattgaact gttaacnttg ggccnggttc cncctnggtg gtctgaaact aatcacgcgc      660
actggaaaaa ggtangtgcc ttcttgaat tcccaaannt cccctngntt tgggtntttt      720
ctcctctncc ctaaaaatcg tnttcccccc cntanggcg      760

```

<210> 38

<211> 724

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(724)

<223> n = A,T,C or G

<400> 38

```

tttttttttt tttttttttt tttttttttt ttttttaaaa cccctccat tgaatgaaaa      60
cttcnaaat tgtccaaccc cctcnccaa atnnccattt ccgggggggg gttccaaacc      120
caaattaatt ttgganttta aattaaatnt tnattngggg aanaanccaa atgtnaagaa      180
aatttaaccc attatnaact taaatnccn gaaaccctg gnttccaaaa atttttaacc      240
cttaaatccc tccgaaattg ntaanggaaa accaaattcn cctaaggctn tttgaagggt      300
ngatttaaac cccttnant tnttttnacc cnngnctnaa ntatttngnt tccggtgttt      360
tcctnttaan cntnggtaac tcccgntaat gaannnccct aanccaatta aaccgaattt      420
tttttgaatt ggaaattccn ngggaattna ccgggggttt tcccntttgg gggccatncc      480
ccnctttcg gggtttggn ntaggttgaa tttttnnang nccccaaaaa ncccccaana      540
aaaaaactcc caagnnttaa ttngaantnc ccccttccca ggccttttgg gaaaggnggg      600
ttnttggggg ccngggantc cnttcccccn ttncncccc ccccccnggt aaanggttat      660
ngnntttggt ttttgggccc cttnanggac cttccgatn gaaattaaat ccccggnccg      720
gccg      724

```

<210> 39

<211> 751

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(751)

<223> n = A,T,C or G

<400> 39

```
<210> 40
<211> 753
<212> DNA
<213> Homo sapien
```

<400> 40

```
<210> 41
<211> 341
<212> DNA
<213> Homo sapien
```

actatatcca	tcacaacaga	catgtttcat	cccatagact	tcttgacata	gcttcaaattg	60
agtgaaccca	tccttgattt	atatacatat	atgtttctcag	tattttggga	gcctttccac	120
ttctttaaac	cttgttcatt	atgaacactg	aaaataggaa	tttgtgaaga	gttaaaaagt	180
tatagcttgt	ttacgtagta	agtttttgaa	gtctacattc	aatccagaca	cttagttgag	240
tgttaaactg	tgatttttaa	aaaatatcat	ttgagaatat	tctttcagag	gtattttcat	300
ttttactttt	tgattaattg	tgttttatat	attagggtag	t		341

<400> 42

<400> 43

<400> 44

<210> 45

<400> 45

<210> 46

<212> DNA

$\langle 220 \rangle$

<222> (1) ... (590)

<400> 46

<210> 47

<211> 774

<212> DNA

<220>

<221> misc feature

 $\langle 222 \rangle \quad (1) \dots (774)$

<400> 47

acaagggggc	ataatgaagg	agtggggana	gattttaaag	aaggaaaaaa	aacgaggccc	60
tgaacagaat	tttctgnac	aacggggctt	caaaataatt	ttcttgggga	ggttcaagac	120
gcttcactgc	ttgaaactta	aatggatgtg	ggacanaatt	ttctgtaatg	accctgaggg	180
cattacagac	gggactctgg	gaggaaggat	aaacagaaag	gggacaaagg	ctaataccaa	240
aacatcaaag	aaaggaaggt	ggcgtcatac	ctcccagcct	acacagttct	ccagggctct	300
cctcatccct	ggaggacgac	agtggaggaa	caactgacca	tgtccccagg	ctcctgtgtg	360
ctggctcctg	gtcttcagcc	cccagctctg	gaagcccacc	ctctgctgat	cctgcgtggc	420
ccacactcct	tgaacacaca	tccccaggtt	atattcctgg	acatggctga	acctcctatt	480

```
<210> 48
<211> 124
<212> DNA
<213> Homo sapien
```

<400> 48

```
<210> 49
<211> 147
<212> DNA
<213> Homo sapien
```

<400> 49

```
<210> 50
<211> 107
<212> DNA
<213> Homo sapien
```

<400> 50

```
<210> 51
<211> 204
<212> DNA
<213> Homo sapien
```

<400> 51

```
<210> 52
<211> 491
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(491)
<223> n = A,T,C or G
```

```
<210> 53
<211> 484
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(484)
<223> n = A,T,C or G
```

```
<210> 54
<211> 151
<212> DNA
<213> Homo sapien
```

<400> 54
 actaaacctc gtgcttgtga actccataca gaaaacggtg ccatccctga acacggctgg 60
 ccactgggta tactgctgac aaccgcaaca acaaaaacac aaatccttgg cactggctag 120
 tctatgtcct ctcaagtgcc tttttgtttg t 151

<210> 55
 <211> 91
 <212> DNA
 <213> Homo sapien

<400> 55
 acctggcttg tctccgggtg gttcccggtg cccccacgg tccccagaac ggacactttc 60
 gccctccagt ggatactcga gccaaagtgg t 91

<210> 56
 <211> 133
 <212> DNA
 <213> Homo sapien

<400> 56
 ggcggatgtg cggttggttat atacaaatat gtcattttat gtaagggact tgagtatact 60
 tggatttttg gtatctgtgg gttgggggga cgggtccagga accaataccc catggatacc 120
 aagggacaac tgt 133

<210> 57
 <211> 147
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(147)
 <223> n = A,T,C or G

<400> 57
 actctggaga acctgagccg ctgctccgcc tctgggatga ggtgatgcan gcngtggcgc 60
 gactgggagc tgagcccttc cctttgcgcc tgcctcagag gattgttgcc gacntgcana 120
 tctcantggg ctggatncat gcagggt 147

<210> 58
 <211> 198
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(198)
 <223> n = A,T,C or G

<400> 58

```

acagggatat aggtttnaag ttattgtnat tgtaaaatac attgaatttt ctgtatactc      60
tgattacata catttatcct ttaaaaaaga tgtaaatctt aatttttatg ccatctatta      120
atttaccaat gagttacctt gtaaatgaga agtcatgata gcactgaatt ttaactagtt      180
ttgacttcta agtttggt                                     198

```

```

<210> 59
<211> 330
<212> DNA
<213> Homo sapien

```

```

<400> 59
acaacaaatg ggttgtagag aagtcttata agcaaaactg gtgatggcta ctgaaaagat      60
ccattgaaaa ttatcattaa tgatttttaa tgacaagtta tcaaaaactc actcaatttt      120
cacctgtgct agcttgctaa aatgggagtt aactctagag caaatatagt atcttctgaa      180
tacagtcaat aaatgacaaa gccagggcct acaggtgggt tccagacttt ccagaccag      240
cagaaggaat ctattttata acatggatct ccgtctgtgc tcaaaatacc taatgatatt      300
tttcgtcttt attggacttc tttgaagagt                                     330

```

```

<210> 60
<211> 175
<212> DNA
<213> Homo sapien

```

```

<400> 60
accgtgggtg ccttctacat tcctgacggc tccttcacca acatctgggt ctacttcggc      60
gtcgtgggct ccttctctt catctcctc cagctgggtg tgctcatcga ctttgcgcac      120
tcctggaacc agcgggtggct gggcaaggcc gaggagtgcg attcccgtgc ctggt       175

```

```

<210> 61
<211> 154
<212> DNA
<213> Homo sapien

```

```

<400> 61
acccactttt tcctcctgtg agcagtctgg acttctcact gctacatgat gagggtgagt      60
ggttggtgct cttcaacagt atcctccctt ttccggatct gctgagccgg acagcagtgc      120
tggactgcac agccccgggg ctccacattg ctgt                                     154

```

```

<210> 62
<211> 30
<212> DNA
<213> Homo sapien

```

```

<400> 62
cgctcgagcc ctatagttag tcgtattaga                                     30

```

```

<210> 63
<211> 89
<212> DNA
<213> Homo sapien

```


<400> 63
acaagtcatt tcagcaccct ttgctcttca aaactgacca tcttttatat ttaatgcttc 60
ctgtatgaat aaaaatggtt atgtcaagt 89

<210> 64
<211> 97
<212> DNA
<213> Homo sapien

<400> 64
accggagtaa ctgagtcggg acgctgaatc tgaatccacc aataaataaa ggttctgcag 60
aatcagtgc tccaggattg gtccttggat ctgggggt 97

<210> 65
<211> 377
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1) ... (377)
<223> n = A,T,C or G

<400> 65
acaacaanaa ntcccttctt taggcactg atggaaacct ggaacccct tttgatggca 60
gcatggcgtc ctaggccttg acacagcggc tggggtttgg gctntccaa accgcacacc 120
ccaaccctgg tctaccaca nttctggcta tgggctgtct ctgccactga acatcaggggt 180
tcggtcataa natgaaatcc caanggggac agaggtcagt agaggaagct caatgagaaa 240
ggtgctgttt gctcagccag aaaacagctg cctggcattc gccgctgaac tatgaacccg 300
tgggggtgaa ctacccccc gaggaatcat gcctgggcga tgcaanggtg ccaacaggag 360
gggcgggagg agcatgt 377

<210> 66
<211> 305
<212> DNA
<213> Homo sapien

<400> 66
acgcctttcc ctcagaattc aggggaagaga ctgtcgctg ccttcctccg ttgttgctg 60
agaaccgtg tgcccttcc caccatatcc accctcgctc catctttgaa ctcaaacacg 120
aggaaactaac tgcaccctgg tcctctcccc agtccccagt tcaccctcca tccctcacct 180
tcctccactc taagggatat caacactgcc cagcacaggg gccctgaatt tatgtggttt 240
ttatatattt ttttaataaga tgcactttat gtcatttttt aataaagtct gaagaattac 300
tgttt 305

<210> 67
<211> 385
<212> DNA
<213> Homo sapien

<400> 67

```

actacacaca ctccacttgc ccttgtgaga cactttgtcc cagcacttta ggaatgctga      60
ggtcggacca gccacatctc atgtgcaaga ttgccagca gacatcaggt ctgagagttc      120
cccttttaaa aaaggggact tgcttaaaaa agaagtctag ccacgattgt gtagagcagc      180
tgtgctgtgc tggagattca cttttgagag agttctcctc tgagacctga tcttttagagg      240
ctgggcagtc ttgcacatga gatggggctg gtctgatctc agcactcctt agtctgcttg      300
cctctcccag ggccccagcc tggccacacc tgcttacagg gcactctcag atgcccatac      360
catagtttct gtgctagtgg accgt                                           385

```

<210> 68

<211> 73

<212> DNA

<213> Homo sapien

<400> 68

```

acttaaccag atatattttt accccagatg gggatattct ttgtaaaaaa tgaaaataaa      60
gttttttttaa tgg                                                         73

```

<210> 69

<211> 536

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(536)

<223> n = A,T,C or G

<400> 69

```

actagtcag tgtggtggaa ttccattgtg ttgggggctc tcaccctcct ctctgcagc      60
tccagctttg tgctctgcct ctgaggagac catggcccag catctgagta ccctgctgct      120
cctgctggcc accctagctg tggccctggc ctggagcccc aaggaggagg ataggataat      180
cccgggtggc atctataacg cagacctcaa tgatgagtgg gtacagcgtg cccttcactt      240
cgccatcagc gagtataaca aggccaccaa agatgactac tacagacgtc cgctgcgggt      300
actaagagcc aggcaacaga ccgttggggg ggtgaattac ttcttcgacg tagagggtggg      360
ccgaaccata tgtaccaagt ccagcccaa cttggacacc tgtgccttcc atgaacagcc      420
agaactgcag aagaaacagt tgtgctcttt cgagatctac gaagttccct ggggagaaca      480
gaangtcctt gggtgaaatc caggtgtcaa gaaatcctan ggatctgttg ccaggc      536

```

<210> 70

<211> 477

<212> DNA

<213> Homo sapien

<400> 70

```

atgacccta acaggggccc tctcagccct cctaattgacc tccggcctag ccatgtgatt      60
tacttccac tccataacgc tctcataact aggcctacta accaaccacac taaccatata      120
ccaatgatgg cgcgatgtaa cagagaaag cacataccaa ggccaccaca caccacctgt      180
ccaaaaaggc cttcgatacg ggataatcct atttattacc tcagaagttt ttttcttcgc      240
agggattttt ctgagccttt taccactcca gcctagcccc taccocccaa ctaggagggc      300
actggcccc aacaggcatc accccgctaa atcccctaga agtcccactc ctaaaccacat      360
ccgtattact cgcatacagga gtatcaatca cctgagctca ccatagtcta atagaaaaca      420
accgaaacca aattattcaa agcactgctt attacaattt tactgggtct ctattttt      477

```

```
<220>
<221> misc_feature
<222> (1) ... (533)
<223> n = A,T,C or G
```

```
<210> 72
<211> 511
<212> DNA
<213> Homo sapien
```

```
<220>
<221> misc_feature
<222> (1)...(511)
<223> n = A,T,C or G
```

```
<210> 73
<211> 499
<212> DNA
<213> Homo sapien
```

```
<220>  
<221> misc_feature  
<222> (1)...(499)
```

<223> n = A,T,C or G

<400> 73

cagtgccagc	actggtgcc	gtaccagtac	caataacagt	gccagtgcc	gtgccagcac	60
cagtgggtggc	ttcagtgtg	gtgccagcct	gaccgccact	ctcacatttg	ggctcttcgc	120
tggccttggt	ggagctggtg	ccagcaccag	tggcagctct	ggcgcctgtg	gtttctccta	180
caagtgagat	tttagatatt	gttaatcctg	ccagtctttc	tcttcaagcc	agggtgcatc	240
ctcagaaacc	tactcaacac	agcactctag	gcagccacta	tcaatcaatt	gaagttgaca	300
ctctgcatta	aatctatttg	ccatttctga	aaaaaaaaaa	aaaaaaagg	cggccgctcg	360
antctagagg	gccccgttaa	acccgctgat	cagcctcgac	tgtgccttct	anttgccagc	420
catctgttgt	ttgccccctc	cccngtgcct	tccttgaccc	tggaaagtgc	cactccctac	480
gtccttttct	aantaaaat					499

<210> 74

<211> 537

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (537)

<223> n = A,T,C or G

<400> 74

tttcatagga	gaacacactg	aggagatact	tgaagaatth	ggattcagcc	gcgaagagat	60
ttatcagctt	aactcagata	aaatcattga	aagtaataag	gtaaaagcta	gtctctaact	120
tccaggccca	cggctcaagt	gaatttgaat	actgcattta	cagtgtagag	taacacataa	180
cattgtatgc	atggaaacat	ggaggaacag	tattacagt	tcctaccact	ctaatacaaga	240
aaagaattac	agactctgat	tctacagtga	tgattgaatt	ctaaaaatgg	taatcattag	300
ggcttttgat	ttataanact	ttgggtactt	atactaaatt	atggtagtta	tactgccttc	360
cagtttgctt	gataatattg	ttgatattaa	gattcttgac	ttatattttg	aatgggttct	420
actgaaaaan	gaatgatata	ttcttgaaaga	catcgatata	catttattta	cactcttgat	480
tctacaatgt	agaaaatgaa	ggaaatgccc	caaattgtat	ggtgataaaa	gtccctgt	537

<210> 75

<211> 467

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (467)

<223> n = A,T,C or G

<400> 75

caaanacaat	tggttcaaaag	atgcaaata	tacactactg	ctgcagctca	caaacacctc	60
tgcataattac	acgtacctcc	tcctgctcct	caagtagtgt	ggctctatth	gccatcatca	120
cctgctgtct	gcttagaaga	acggctttct	gctgcaangg	agagaaatca	taacagacgg	180
tggcacaagg	aggccatctt	ttcctcatcg	gttattgtcc	ctagaagcgt	cttctgagga	240
tctagttggg	ctttctttct	gggtttgggc	catttcantt	ctcatgtgtg	tactattcta	300
tcattattgt	ataacggth	tcaaaccngt	gggcacncag	agaacctcac	tctgtaataa	360

```

caatgaggaa tagccacggt gatctccagc accaaatctc tccatgttnt tccagagctc 420
ctccagccaa cccaaatagc cgctgctatn gtgtagaaca tccttgn 467

```

```

<210> 76
<211> 400
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(400)
<223> n = A,T,C or G

```

```

<400> 76
aagctgacag cattcgggcc gagatgtctc gctccgtggc cttagctgtg ctgcgctac 60
tctctctttc tggcctggag gctatccagc gtactccaaa gattcagggt tactcacgtc 120
atccagcaga gaatggaaa tcaaatttcc tgaattgcta tgtgtctggg ttcatccat 180
ccgacattga agttgactta ctgaagaatg gagagagaat tgaaaaagt gagcattcag 240
acttgtcttt cagcaaggac tggctcttct atctcttgta ctacactgaa ttcaccccca 300
ctgaaaaaga tgagtatgcc tgccgtgtga accatgtgac tttgtcacag cccaagatng 360
ttnagtggga tcganacatg taagcagcan catgggaggt 400

```

```

<210> 77
<211> 248
<212> DNA
<213> Homo sapien

```

```

<400> 77
ctggagtgcc ttggtgtttc aagccctgc aggaagcaga atgcaccttc tgaggcacct 60
ccagctgccc cggcggggga tgcgaggctc ggagcacctc tgcccggctg tgattgctgc 120
caggcactgt tcatctcagc ttttctgtcc ctttgctccc ggcaagcgct tctgctgaaa 180
gttcatatct ggagcctgat gtcttaacga ataaaggctc catgctccac ccgaaaaaaa 240
aaaaaaaa 248

```

```

<210> 78
<211> 201
<212> DNA
<213> Homo sapien

```

```

<400> 78
actagtccag tgtggtggaa ttccattgtg ttgggcccac cacaatggct acctttaaca 60
tcaccagac cccgccctgc ccgtgcccc cgtgctgct aacgacagta tgatgcttac 120
tctgctactc ggaaactatt tttatgtaat taatgtatgc tttcttgttt ataaatgcct 180
gatttaaaaa aaaaaaaaaa a 201

```

```

<210> 79
<211> 552
<212> DNA
<213> Homo sapien

```

```

<220>

```

<221> misc_feature
 <222> (1)...(552)
 <223> n = A,T,C or G

<400> 79
 tccttttgtt aggtttttga gacaacccta gacctaaact gtgtcacaga cttctgaatg 60
 tttaggcagt gctagtaatt tcctcgtaat gattctgtta ttactttcct attctttatt 120
 cctctttcct ctgaagatta atgaagtga aaattgaggt ggataaatac aaaaaggtag 180
 tgtgatagta taagtatcta agtgcagatg aaagtgtgtt atatatatcc attcaaaatt 240
 atgcaagtta gtaattactc agggtttaact aaattacttt aatatgctgt tgaacctact 300
 ctgttccttg gctagaaaaa attataaaca ggactttgtt agtttgggaa gccaaattga 360
 taatattcta tgttctaaaa gttgggctat acataaanta tnaagaaata tggaatttta 420
 ttcccaggaa tatgggggttc atttatgaat antaccggg anagaagttt tgantnaaac 480
 cngtttttgt taatacgta atatgtcctn aatnaacaag gcntgactta tttccaaaaa 540
 aaaaaaaaaa aa 552

<210> 80
 <211> 476
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(476)
 <223> n = A,T,C or G

<400> 80
 acagggattt gagatgctaa ggccccagag atcgtttgat ccaaccctct tattttcaga 60
 ggggaaaatg gggcctagaa gttacagagc atctagctgg tgcgctggca cccctggcct 120
 cacacagact cccgagtagc tgggactaca ggcacacagt cactgaagca ggccctgttt 180
 gcaattcacg ttgccacctc caacttaaac attcttcata tgtgatgtcc ttagtacta 240
 aggttaaaact ttcccacca gaaaaggcaa cttagataaa atcttagagt actttcatac 300
 tcttctaagt cctcttcag cctcactttg agtcctcctt ggggggtgat aggaantntc 360
 tcttggtttt ctcaataaaa tctctatcca tctcatgttt aatttggtac gcntaaaaat 420
 gctgaaaaaa ttaaaatggt ctggtttcnc tttaaaaaaa aaaaaaaaaa aaaaaa 476

<210> 81
 <211> 232
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(232)
 <223> n = A,T,C or G

<400> 81
 tttttttttg tatgccntcn ctgtgnggtt attgttgctg ccaccctgga ggagccaggt 60
 ttcttctgta tctttctttt ctggggggtc ttcttggtc tgcccctcca ttcccagcct 120
 ctcacccca tcttgcaact ttgctagggg tggaggcgct ttcttggtag cccctcagag 180
 actcagtcag cggaataaag tcctaggggt ggggggtgtg gcaagccggc ct 232

<210> 82
 <211> 383
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(383)
 <223> n = A,T,C or G

<400> 82
 aggcgggagc agaagctaaa gccaaagccc aagaagagtg gcagtgccag cactggtgcc 60
 agtaccagta ccaataacat gccagtgcc gtgccagcac cagtgggtggc ttcagtgtg 120
 gtgccagcct gaccgccact ctcacatttg ggctcttcgc tggccttggg ggagctggtg 180
 ccagcaccag tggcagctct ggtgcctgtg gtttctccta caagtgagat tttagatatt 240
 gttaatcctg ccagtctttc tcttcaagcc aggggtgcac ctcagaaacc tactcaacac 300
 agcactctng gcagccacta tcaatcaatt gaagttgaca ctctgcatta aatctatttg 360
 ccatttcaaa aaaaaaaaaa aaa 383

<210> 83
 <211> 494
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(494)
 <223> n = A,T,C or G

<400> 83
 accgaattgg gaccgctggc ttataagcga tcatgtcttc cagtattacc tcaacgagca 60
 gggagatcga gtctatacgc tgaagaaatt tgacccgatg ggacaacaga cctgctcagc 120
 ccatcctgct cggttctccc cagatgacaa atactctcga caccgaatca ccatcaagaa 180
 acgcttcaag gtgctcatga cccagcaacc gcgcctctgc ctctgagggg ccttaaactg 240
 atgtcttttc tgccacctgt taccctctcg agactccgta accaaactct tcggactgtg 300
 agccctgatg cctttttgcc agccatactc tttggcntcc agtctctcgt ggcgattgat 360
 tatgcttgtg tgaggcaatc atggtggcat caccatnaa gggaacacat ttganttttt 420
 tttcncatat tttaaattac naccagaata nttcagaata aatgaattga aaaactctta 480
 aaaaaaaaaa aaaa 494

<210> 84
 <211> 380
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(380)
 <223> n = A,T,C or G

<400> 84

```

gctggtagcc tatggcgtgg ccacggangg gctcctgagg cacgggacag tgacttccca      60
agtatcctgc gccgcgtctt ctaccgtccc tacctgcaga tcttcgggca gattccccag      120
gaggacatgg acgtggccct catggagcac agcaactgct cgtcggagcc cggcttctgg      180
gcacaccctc ctggggccca ggcgggcacc tgcgtctccc agtatgcaa ctggctggtg      240
gtgctgctcc tcgtcatctt cctgctcgtg gccaacatcc tgctggtcac ttgctcattg      300
ccatgttcag ttacacattc ggcaaagtac agggcaacag cnatctctac tgggaaggcc      360
agcgttnccg cctcatccgg

```

<210> 85

<211> 481

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(481)

<223> n = A,T,C or G

<400> 85

```

gagttagctc ctccacaacc ttgatgaggt cgtctgcagt ggctctctgc ttcataccgc      60
tnccatcgtc atactgtagg tttgccacca cctcctgcat cttggggcg gctaatatcca      120
ggaaactctc aatcaagtca ccgtcnatna aacctgtggc tggttctgtc ttccgctcgg      180
tgtgaaagga tctccagaag gagtgtctga tcttccccac acttttgatg actttattga      240
gtcgattctg catgtccagc aggaggttgt accagctctc tgacagtgag gtcaccagcc      300
ctatcatgcc nttgaacgtg ccgaagaaca ccgagccttg tgtggggggg gnagtctcac      360
ccagattctg cattaccaga nagccgtggc aaaaganatt gacaactcgc ccaggngaa      420
aaagaacacc tcctggaagt gctngccgct cctcgctcct tgggtggngc gcntnccttt      480
t

```

<210> 86

<211> 472

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(472)

<223> n = A,T,C or G

<400> 86

```

aacatcttcc tgtataatgc tgtgtaatat cgatccgatn ttgtctgctg agaattcatt      60
acttgaaaaa gcaacttnaa gcctggacac tgggtattaaa attcacaata tgcaaacatt      120
taaacagtgt gtcaatctgc tcccttactt tgtcatcacc agtctgggaa taagggtatg      180
ccctattcac acctgttaaa agggcgctaa gcatttttga ttcaacatct ttttttttga      240
cacaagtccg aaaaaagcaa aagtaaacag ttnttaattt gttagccaat tcactttctt      300
catgggacag agccatttga tttaaaaagc aaattgcata atattgagct ttgggagctg      360
atatntgagc ggaagantag cctttctact tcaccagaca caactccttt catattggga      420
tgttnacnaa agttatgtct cttacagatg ggatgctttt gtggcaattc tg

```

<210> 87


```
<220>
<221> misc_feature
<222> (1)...(413)
<223> n = A,T,C or G
```

```
<210> 88
<211> 448
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(448)
<223> n = A,T,C or G
```

```
<210> 89
<211> 463
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(463)
<223> n = A,T,C or G
```

<400> 89
gaattttgtg cactggccac tgtgatggaa ccattgggcc aggatgcttt gagtttatca 60
gtagtatttc tgccaaagtt ggtgttgtaa catgagtatg taaaatgtca aaaaattagc 120

```
<210> 90
<211> 400
<212> DNA
<213> Homo sapien
```

<400>	90							
ctgaa	ggctctntnt	actgtcggac	tgttcacca	ccaactctac	aagttgctgt			60
actca	ctgtctgtaa	gcntnttaac	ccagactgta	tcttcataaa	tagaacaaat			120
accag	tcacatcttc	taggaccttt	ttggattcag	ttagtataag	ctcttccact			180
ctgta	agacttcctc	tggtaaagtc	ttaagttttg	tagaaaggaa	tttaattgct			240
cttaa	caatgtcttc	tccttgaagt	atttggctga	acaacccacc	tnaagtcctt			300
catcc	attttaaata	tacttaatag	ggcattggtn	cactaggtta	aattctgcaa			360
atctg	tctgcaaaaag	ttgcgttagt	atatctgcc					400

<400> 91						
cgga	ccaataatct	ttgtctgagg	gcagcacaca	tatncagtgc	catggnaact	60
acccc	acatgggagc	agcatgccgt	agntatataa	ggtcattccc	tgagtcagac	120
ctttt	gactaccgtg	tgccagtgtc	ggtgattctc	acacacctcc	nncgcgtctt	180
aaaaa	ctggcacttg	netggaacta	gcaagacatc	acttacaaat	tcaccacaga	240
ttgaa	aggtgtaaca	aagcgactct	tgcatgtgct	tttgtccctc	cggcaccagt	300
atact	aaccgcgtgg	tttgctcca	tcacatttgt	gatctgtagc	tctggataca	360
tgaca	gtactgaaga	acttcttctt	ttgtttcaaa	agcaactctt	ggtgctgtt	420
aggtt	cccatttccc	agtccgaatg	ttcacatggc	atatnttact	tcccacaaaa	480

```
<210> 92
<211> 477
<212> DNA
<213> Homo sapien
```

<220>
 <221> misc_feature
 <222> (1)...(477)
 <223> n = A,T,C or G

<400> 92
 atacagccca natcccacca cgaagatgcg cttgttgact gagaacctga tgcggtcact 60
 ggtcccgcctg tagccccagc gactctccac ctgctggaag cggttgatgc tgcactcctt 120
 cccacgcagg cagcagcggg gccggtcaat gaactccact cgtggcttgg ggttgacggg 180
 taantgcagg aagaggctga ccacctcgcg gtccaccagg atgcccgact gtgcgggacc 240
 tgcagcgaaa ctctcgatg gtcatgagcg ggaagcgaat gangcccagg gccttgccca 300
 gaaccttccg cctgttctct ggcgtcacct gcagctgctg ccgctnacac tcggcctcgg 360
 accagcggac aaacggcggt gaacagccgc acctcacgga tgcccantgt gtcgcgctcc 420
 aggaacggcn ccagcgtgtc caggtcaatg tcggtgaanc ctccgcgggt aatggcg 477

<210> 93
 <211> 377
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(377)
 <223> n = A,T,C or G

<400> 93
 gaacggctgg accttgctc gcattgtgct gctggcagga ataccttggc aagcagctcc 60
 agtccgagca gcccagacc gctgccgcc gaagctaagc ctgcctctgg cttccccctc 120
 cgcctcaatg cagaaccant agtgggagca ctgtgttttag agttaagagt gaacactgtn 180
 tgattttact tgggaatttc ctctgttata tagcttttcc caatgctaata ttccaaacaa 240
 caacaacaaa ataacatgtt tgccctgttna gttgtataaa agtangtgat tctgtatnta 300
 aagaaaatat tactgttaca tatactgctt gcaanttctg tatttattgg tncctctggaa 360
 ataaatatat tattaata 377

<210> 94
 <211> 495
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(495)
 <223> n = A,T,C or G

<400> 94
 ccctttgagg ggttagggc cagttcccag tggaagaaac aggccaggag aantgcgtgc 60
 cgagctgang cagatttccc acagtgacct cagagccctg ggctatagtc tctgaccctt 120
 ccaaggaaaag accaccttct ggggacatgg gctggagggc aggacctaga ggcaccaagg 180
 gaaggcccca ttccggggct gttccccgag gaggaaggga aggggctctg tgtgcccccc 240
 acgaggaana ggccctgant cctgggatca nacaccctt cacgtgtatc cccacacaaa 300
 tgcaagctca ccaaggtccc ctctcagtc cttccctaca ccctgaacgg ncactggccc 360

```

acaccacccc agancancca cccgccatgg ggaatgtinct caaggaatcg cngggcaacg      420
tggaactctng tcccnnaagg gggcagaatc tccaatagan gganngaacc cttgctnana      480
aaaaaaaaana aaaaaa                                     495

```

```

<210> 95
<211> 472
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(472)
<223> n = A,T,C or G

```

```

<400> 95
ggttacttgg tttcattgcc accacttagt ggatgtcatt tagaaccatt ttgtctgctc      60
cctctggaag ccttgccgag agcggacttt gtaattgttg gagaataact gctgaatttt      120
tagctgtttt gagttgattc gcaccactgc accacaactc aatatgaaaa ctatttnact      180
tatttattat cttgtgaaaa gtatacaatg aaaattttgt tcatactgta tttatcaagt      240
atgatgaaaa gcaatagata tatattcttt tattatgttn aattatgatt gccattatta      300
atcggcaaaa tgtggagtggt atgttctttt cacagtaata tatgcctttt gtaacttcac      360
ttgggttattt tattgtaaat gaattacaaa attcttaatt taagaaaatg gtangttata      420
tttanttcan taatttcttt ccttgtttac gttaattttg aaaagaatgc at              472

```

```

<210> 96
<211> 476
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(476)
<223> n = A,T,C or G

```

```

<400> 96
ctgaagcatt tcttcaaact tntctacttt tgtcattgat acctgtagta agttgacaat      60
gtggtgaaat ttcaaaaatta tatgtaactt ctactagttt tacttttctcc cccaagtctt      120
ttttaactca tgattttttac acacacaatc cagaacttat tatatagcct ctaagtcttt      180
attcttcaca gtagatgatg aaagagtoct ccagtgtctt gngcanaatg ttctagntat      240
agctggatac atacngtggg agttctataa actcatacct cagtgggact naaccaaaat      300
tgtgttagtc tcaattccta ccacactgag ggagcctccc aaatcactat attcttatct      360
gcaggtaact ctccagaaaa acngacaggg caggcttgca tgaaaaagtn acatctgcgt      420
tacaaagtct atcttcctca nangtctgtn aaggaacaat ttaatcttct agcttt      476

```

```

<210> 97
<211> 479
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature

```

<222> (1)...(479)

<223> n = A,T,C or G

<400> 97

actcttttcta	atgctgatat	gatcttgagt	ataagaatgc	atatgtcact	agaatggata	60
aaataatgct	gcaaacttaa	tgttcttatg	caaaatggaa	cgctaataa	acacagctta	120
caatcgcaaa	tcaaaaactca	caagtgtcca	tctgtttag	atttagtgta	ataagactta	180
gattgtgctc	cttcggatat	gattgtttct	canatcttgg	gcaatnttcc	ttagtcaa	240
caggctacta	gaattctgtt	attggatatn	tgagagcatg	aaatTTTTaa	naatacactt	300
gtgattatna	aattaatcac	aaatttccact	tatacctgct	atcagcagct	agaaaaacat	360
ntnnttttta	natcaaagta	ttttgtgttt	ggaantgttn	aaatgaaatc	tgaatgtggg	420
ttcnatctta	ttttttcccn	gacnactant	tnctttttta	gggnctattc	tgancctatc	479

<210> 98

<211> 461

<212> DNA

<213> Homo sapien

<400> 98

agtgacttgt	cctccaacaa	aacccttga	tcaagtttgt	ggcactgaca	atcagacctta	60
tgctagttcc	tgctatctat	tcgtactaa	atgcagactg	gaggggacca	aaaaggggca	120
tcaactccag	ctggattatt	ttggagcctg	caaactctatt	cctacttgta	cggactttga	180
agtgattcag	tttctctac	ggatgagaga	ctggctcaag	aatatcctca	tgacgcttta	240
tgaagccact	ctgaacacgc	tggttatcta	gatgagaaca	gagaaataaa	gtcagaaaat	300
ttacctggag	aaaagaggct	ttggctgggg	accatcccat	tgaaccttct	cttaaggact	360
ttaagaaaaa	ctaccacatg	ttgtgtatcc	tggtgccggc	cgtttatgaa	ctgaccaccc	420
tttgaataaa	tcttgacgct	cctgaacttg	ctcctctgcg	a		461

<210> 99

<211> 171

<212> DNA

<213> Homo sapien

<400> 99

gtggccgcgc	gcaggtgttt	cctcgtaaccg	cagggccccc	tccttcccc	aggcgctcct	60
cggcgctct	gcgggcccga	ggaggagcgg	ctggcggtg	gggggagtgt	gaccaccct	120
cggtgagaaa	agccttctct	agcgatctga	gaggcggtgc	ttgggggtac	c	171

<210> 100

<211> 269

<212> DNA

<213> Homo sapien

<400> 100

cggccgcaag	tgcaactcca	gctggggccg	tgccgacgaa	gattctgcca	gcagttggtc	60
cgactgcgac	gacggcgggc	gcgacagtcg	caggtgcagc	gcggggcgct	ggggtcttgc	120
aaggctgagc	tgacgccgca	gaggtcgtgt	cacgtccac	gaccttgacg	ccgtcgggga	180
cagccggaac	agagcccggg	gaagcgggag	gcctcgggga	gcccctcggg	aaggcgggcc	240
cgagagatac	gcaggtgcag	gtggccgcgc				269

<210> 101

<211> 405
 <212> DNA
 <213> Homo sapien

<400> 101
 tttttttttt ttttggaaatc tactgcgagc acagcaggtc agcaacaagt ttatttttgca 60
 gctagcaagg taacagggtta gggcatgggtt acatgttcag gtcaacttcc tttgtcgtgg 120
 ttgattgggtt tgtctttatg ggggcgggggt ggggtagggg aaacgaagca aataacatgg 180
 agtgggtgca ccctccctgt agaacctgggt taaaaagctt ggggcagttc acctggtctg 240
 tgaccgtcat tttcttgaca tcaatgttat tagaagtcag gatattcttt agagagtcca 300
 ctgttctgga gggagattag ggtttcttgc caaatccaac aaaatccact gaaaaagttg 360
 gatgatcagt acgaataaccg aggcataatc tcatatcggt ggcca 405

<210> 102
 <211> 470
 <212> DNA
 <213> Homo sapien

<400> 102
 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 60
 ggcacttaat ccattttttat ttcaaaatgt ctacaaattht aatcccatta tacgggtattt 120
 tcaaaatcta aattattcaa attagccaaa tcctttacca ataataccca aaaatcaaaa 180
 atatacttct ttcagcaaac ttgtttacata aattaaaaaa atatatacgg ctggtgtttt 240
 caaagtacaa ttatcttaac actgcaaaca ttttaaggaa ctaaaataaa aaaaaacact 300
 ccgcaaaggt taaagggaac aacaaattct tttacaacac cattataaaa atcatatctc 360
 aaatcttagg ggaatatata cttcacacgg gatcttaact tttactcact ttgtttattt 420
 ttttaaacca ttgtttgggc ccaacacaat ggaatcccc ctggactagt 470

<210> 103
 <211> 581
 <212> DNA
 <213> Homo sapien

<400> 103
 tttttttttt ttttttttga cccccctctt ataaaaaaca agttaccatt ttattttact 60
 tacacatatt tattttataa ttgggtattag atattcaaaa ggcagctttt aaaatcaaac 120
 taaatggaaa ctgccttaga tacataattc ttaggaatta gcttaaaatc tgcctaaagt 180
 gaaaatcttc tctagctctt ttgactgtaa atttttgact cttgtaaaac atccaaattc 240
 atttttcttg tctttaaatt tatctaattc ttccattttt tccctattcc aagtcaattt 300
 gcttctctag cctcatthtc tagctcttat ctactattag taagtggctt ttttcctaaa 360
 agggaaaaca ggaagagaaa tggcacacaa aacaaacatt ttatattcat atttctacct 420
 acgttaataa aatagcattt tgtgaagcca gctcaaaaga aggcttagat ccttttatgt 480
 ccatttttagt cactaaacga tatcaaagtg ccagaatgca aaaggtttgt gaacatttat 540
 tcaaaagcta atataagata tttcacatac tcatctttct g 581

<210> 104
 <211> 578
 <212> DNA
 <213> Homo sapien

<400> 104

tttttttttt	tttttttttt	tttttctctt	cttttttttt	gaaatgagga	tcgagttttt	60
cactctctag	atagggcatg	aagaaaactc	atctttccag	ctttaaaata	acaatcaa	120
ctcttatgct	atatcatatt	ttaagttaaa	ctaatagagc	actggcttat	cttctcctga	180
aggaaatctg	ttcattcttc	tcattcatat	agttatatca	agtactacct	tgcatattga	240
gaggtttttc	ttctctat	acacatatat	ttccatgtga	atttgatatca	aacctttatt	300
ttcatgcaaa	ctagaaaata	atgtttcttt	tgcataagag	aagagaacaa	tatagcatta	360
caaaactgct	caaattgttt	gttaagttaa	ccattataat	tagttggcag	gagctaatac	420
aaatcacatt	tacgacagca	ataataaaac	tgaagtacca	gttaaataatc	caaaataatt	480
aaaggaacat	ttttagcctg	ggtataatta	gctaattcac	tttacaagca	tttattagaa	540
tgaattcaca	tggtattatt	cctagcccaa	cacaatgg			578

<210> 105

<211> 538

<212> DNA

<213> Homo sapien

<400> 105

tttttttttt	tttttcagta	ataatcagaa	caatatttat	ttttatattt	aaaattcata	60
gaaaagtgcc	ttacatttaa	taaaagtttg	tttctcaaag	tgatcagagg	aattagatat	120
gtcttgaaca	ccaatattaa	tttgaggaaa	atacaccaaa	atacattaag	taaattattt	180
aagatcatag	agcttgtaag	tgaaaagata	aaatttgacc	tcagaaaactc	tgagcattaa	240
aaatccacta	ttagcaata	aattactatg	gacttcttgc	tttaattttg	tgatgaatat	300
ggggtgtcac	tggtaaacca	acacattctg	aaggatacat	tacttagtga	tagattctta	360
tgtactttgc	taatacgtgg	atatgagttg	acaagtttct	ctttcttcaa	tcttttaagg	420
ggcgagaaat	gaggaagaaa	agaaaaggat	tacgcatact	gttcttttcta	tggaaggatt	480
agatatgttt	cctttgccaa	tattaaaaaa	ataataatgt	ttactactag	tgaaaccc	538

<210> 106

<211> 473

<212> DNA

<213> Homo sapien

<400> 106

tttttttttt	tttttttagtc	aagtttctat	ttttattata	attaaagtct	tggtcatttc	60
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tttataaatg	taaggtgcca	ttattgagta	atatattcct	ccaagagtgg	atgtgtccct	180
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<210> 107

<211> 1621

<212> DNA

<213> Homo sapien

<400> 107

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<210> 108

<211> 382

<212> PRT

<213> Homo sapien

<400> 108

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Arg Val Asp Arg Pro Gly Ser Arg Tyr Asp Val Ser Arg Leu Gly Arg
35          40          45
Gly Lys Arg Ser Leu Val Leu Asp Leu Lys Gln Pro Arg Gly Ala Ala
50          55          60
Val Leu Arg Arg Leu Cys Lys Arg Ser Asp Val Leu Leu Glu Pro Phe
65          70          75          80
Arg Arg Gly Val Met Glu Lys Leu Gln Leu Gly Pro Glu Ile Leu Gln
85          90          95
Arg Glu Asn Pro Arg Leu Ile Tyr Ala Arg Leu Ser Gly Phe Gly Gln
100         105         110
Ser Gly Ser Phe Cys Arg Leu Ala Gly His Asp Ile Asn Tyr Leu Ala
115         120         125
Leu Ser Gly Val Leu Ser Lys Ile Gly Arg Ser Gly Glu Asn Pro Tyr
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<210> 110

<211> 3410

<212> DNA

<213> Homo sapien

<400> 110

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<210> 111

<211> 1289

<212> DNA

<213> Homo sapien

<400> 111

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<210> 112
<211> 315
<212> PRT
<213> Homo sapien
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<210> 113

<211> 553
 <212> PRT
 <213> Homo sapien

<400> 113

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Ala	Ala	Gly	Ile	Thr	Tyr	Val	Pro	Pro	Leu	Leu	Leu	Glu	Val	Gly	Val
		35					40					45			
Glu	Glu	Lys	Phe	Met	Thr	Met	Val	Leu	Gly	Ile	Gly	Pro	Val	Leu	Gly
	50					55					60				
Leu	Val	Cys	Val	Pro	Leu	Leu	Gly	Ser	Ala	Ser	Asp	His	Trp	Arg	Gly
65					70				75						80
Arg	Tyr	Gly	Arg	Arg	Arg	Pro	Phe	Ile	Trp	Ala	Leu	Ser	Leu	Gly	Ile
			85						90					95	
Leu	Leu	Ser	Leu	Phe	Leu	Ile	Pro	Arg	Ala	Gly	Trp	Leu	Ala	Gly	Leu
			100					105					110		
Leu	Cys	Pro	Asp	Pro	Arg	Pro	Leu	Glu	Leu	Ala	Leu	Leu	Ile	Leu	Gly
		115					120					125			
Val	Gly	Leu	Leu	Asp	Phe	Cys	Gly	Gln	Val	Cys	Phe	Thr	Pro	Leu	Glu
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Ala	Leu	Leu	Ser	Asp	Leu	Phe	Arg	Asp	Pro	Asp	His	Cys	Arg	Gln	Ala
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Tyr	Ser	Val	Tyr	Ala	Phe	Met	Ile	Ser	Leu	Gly	Gly	Cys	Leu	Gly	Tyr
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Leu	Leu	Pro	Ala	Ile	Asp	Trp	Asp	Thr	Ser	Ala	Leu	Ala	Pro	Tyr	Leu
			180					185					190		
Gly	Thr	Gln	Glu	Glu	Cys	Leu	Phe	Gly	Leu	Leu	Thr	Leu	Ile	Phe	Leu
	195						200					205			
Thr	Cys	Val	Ala	Ala	Thr	Leu	Leu	Val	Ala	Glu	Glu	Ala	Ala	Leu	Gly
	210					215					220				
Pro	Thr	Glu	Pro	Ala	Glu	Gly	Leu	Ser	Ala	Pro	Ser	Leu	Ser	Pro	His
225					230					235					240
Cys	Cys	Pro	Cys	Arg	Ala	Arg	Leu	Ala	Phe	Arg	Asn	Leu	Gly	Ala	Leu
				245					250					255	
Leu	Pro	Arg	Leu	His	Gln	Leu	Cys	Cys	Arg	Met	Pro	Arg	Thr	Leu	Arg
			260					265					270		
Arg	Leu	Phe	Val	Ala	Glu	Leu	Cys	Ser	Trp	Met	Ala	Leu	Met	Thr	Phe
		275					280					285			
Thr	Leu	Phe	Tyr	Thr	Asp	Phe	Val	Gly	Glu	Gly	Leu	Tyr	Gln	Gly	Val
	290					295					300				
Pro	Arg	Ala	Glu	Pro	Gly	Thr	Glu	Ala	Arg	Arg	His	Tyr	Asp	Glu	Gly
305					310					315					320
Val	Arg	Met	Gly	Ser	Leu	Gly	Leu	Phe	Leu	Gln	Cys	Ala	Ile	Ser	Leu
				325					330					335	
Val	Phe	Ser	Leu	Val	Met	Asp	Arg	Leu	Val	Gln	Arg	Phe	Gly	Thr	Arg
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Ala	Val	Tyr	Leu	Ala	Ser	Val	Ala	Ala	Phe	Pro	Val	Ala	Ala	Gly	Ala
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Ser Pro Tyr Phe Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn
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 180 185 190
 His Asp Gln Lys Val Glu Gly Cys Phe Asn Gln Leu Leu Tyr Asp Ile
 195 200 205
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<210> 115
 <211> 366
 <212> DNA
 <213> Homo sapien

<400> 115
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 ttggtttgtg aatccatctt gctttttccc cattggaact agtcattaac ccatctctga 180
 actggtagaa aaacatctga agagctagtc tatcagcatc tgacaggtga attggatggt 240
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<210> 116
 <211> 282
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(282)
 <223> n = A,T,C or G

<400> 116
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 agactttact attttcatat tttaagacac atgatttatc ctatttttagt aacctgggtc 180
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<210> 117
 <211> 305
 <212> DNA
 <213> Homo sapien

<220>
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<223> n = A, T, C or G

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tactgatccc	tgatcactgt	cctaatgcag	gatgtgggaa	acagatgagg	tcacctctgt	240
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<213> Homo sapien

<223> n = A, T, C or G

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<213> Homo sapien

<223> n = A, T, C or G

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<213> Homo sapien

<223> n = A, T, C or G

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<210> 121
 <211> 218
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(218)
 <223> n = A,T,C or G

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 atatncangt aaattangga atgaattcat ggttcctttg ggaattcctt tacgatngcc 180
 agcatanact tcatgtgggg atancagcta cccttgta 218

<210> 122
 <211> 171
 <212> DNA
 <213> Homo sapien

<400> 122
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<210> 123
 <211> 76
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(76)
 <223> n = A,T,C or G

<400> 123
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<210> 124
 <211> 131
 <212> DNA
 <213> Homo sapien

<400> 124
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caatgtgctg ggtcatatgg aggggaggag actctaaaat agccaatttt attctcttgg 120
ttaagatttg t 131

<210> 125
<211> 432
<212> DNA
<213> Homo sapien

<400> 125
actttatcta ctggctatga aatagatggg ggaaaattgc gttaccaact ataccactgg 60
cttgaaaaag aggtgatagc tcttcagagg acttgtgact ttgctcaga tgctgaagaa 120
ctacagtctg catttggcag aaatgaagat gaatttggat taaatgagga tgctgaagat 180
ttgcctcacc aaacaaaagt gaaacaactg agagaaaatt ttcaggaaaa aagacagtgg 240
ctcttgaaagt atcagtcact ttgagaatg tttcttagtt actgcatact tcatggatcc 300
catggtgggg gtcttgcac tgtaagaatg gaattgattt tgcttttgca agaattctcag 360
caggaaacat cagaaccact attttctagc cctctgtcag agcaaaccctc agtgcctctc 420
ctcttttgctt gt 432

<210> 126
<211> 112
<212> DNA
<213> Homo sapien

<400> 126
acacaacttg aatagtaaaa tagaaactga gctgaaattt ctaattcact ttctaaccat 60
agtaagaatg atatttcccc ccagggatca ccaaattatt ataaaaattt gt 112

<210> 127
<211> 54
<212> DNA
<213> Homo sapien

<400> 127
accacgaaac cacaacaag atggaagcat caatccactt gccaaagcaca gcag 54

<210> 128
<211> 323
<212> DNA
<213> Homo sapien

<400> 128
acctcattag taattgtttt gttgtttcat ttttttctaa tgtctcccct ctaccagctc 60
acctgagata acagaatgaa aatggaagga cagccagatt tctcctttgc tctctgctca 120
ttctctctga agtctaggtt acccatTTTTT gggaccatt ataggcaata aacacagttc 180
ccaaagcatt tggacagttt cttgttgtgt tttagaatgg ttttcctttt tcttagcctt 240
ttcctgcaaa aggtcactc agtcccttgc ttgctcagtg gactgggctc cccagggcct 300
aggctgcctt cttttccatg tcc 323

<210> 129
<211> 192
<212> DNA

002690-002690

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(192)

<223> n = A,T,C or G

<400> 129

acatacatgt	gtgtatat	tttaaata	cttttgta	actctgac	tttagcata	60
tgaaaacaca	ctaacata	ttntgtga	catgatcag	tacaaccca	atcattcat	120
tagcacattc	atctgtga	naaagata	tgagtttcat	ttccttcac	ttggccaat	180
gataaaca	gt					192

<210> 130

<211> 362

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(362)

<223> n = A,T,C or G

<400> 130

ccctttttta	tggaatgag	agactgtat	tttgaanat	tanccaca	ctctttgac	60
tataatgacg	caacaaaa	gtgctgttt	gtcctatgg	tcagtttat	cccctgaca	120
gtttccattg	tgttttgcc	atcttctgg	taatcgtgg	atcctccat	ttattagta	180
ttctgtattc	cattttgtt	acgcctgg	gatgtaacc	gctangagg	taactttat	240
cttattttaa	agctcttat	ttgtgggtc	taaaatgg	atttatgtg	agcactttt	300
tgcagcagga	agcacgtgt	ggttgggtt	aaagctctt	gctaattct	aaaagtaat	360
gg						362

<210> 131

<211> 332

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(332)

<223> n = A,T,C or G

<400> 131

ctttttgaaa	gatcgtgtc	actcctgtg	acatcttgt	ttaatggag	ttcccatgc	60
gtangactgg	tatggttgc	gctgtccag	taaaaacat	tgaagagtc	caaaatgag	120
gttctcccag	gttcgccct	ctgctccaa	tctcagcag	agcctcttt	aggaggcat	180
ttctgaacta	gattaaggc	gcttgtaaa	ctgatgtgat	ttggtttatt	atccaactaa	240
cttccatctg	ttatcactg	agaaagccc	gactcccan	gacnggtac	gattgtggg	300
atanaaggat	tgggtgaag	tggcgttgt	gt			332

<210> 132

<211> 322
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(322)
 <223> n = A,T,C or G

<400> 132
 acttttgcca ttttgtatat ataaacaatc ttgggacatt ctcttgaaaa ctaggtgtcc 60
 agtgggctaag agaactcgat ttcaagcaat tctgaaagga aaaccagcat gacacagaat 120
 ctcaaattcc caaacagggg ctctgtggga aaaatgaggg aggaccttg tatctcgggt 180
 tttagcaagt taaaatgaan atgacaggaa aggcttattt atcaacaaag agaagagttg 240
 ggatgcttct aaaaaaaact ttggtagaga aaataggaat gctnaatcct agggaagcct 300
 gtaacaatct acaattgggc ca 322

<210> 133
 <211> 278
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(278)
 <223> n = A,T,C or G

<400> 133
 acaagccttc acaagtttaa ctaaattggg attaatcttt ctgtanttat ctgcataatt 60
 cttgtttttc tttccatctg gctcctgggt tgacaatttg tggaaacaac tctattgcta 120
 ctatttaaaa aaaatcacaa atctttccct ttaagctatg ttnaattcaa actattcctg 180
 ctattcctgt tttgtcaaag aaattatatt tttcaaaata tgtntatttg tttgatgggt 240
 cccacgaaac actaataaaa accacagaga ccagcctg 278

<210> 134
 <211> 121
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(121)
 <223> n = A,T,C or G

<400> 134
 gtttanaaaa cttgttttagc tccatagagg aaagaatggt aaactttgta ttttaaaaca 60
 tgattctctg aggttaaact tgggttttcaa atgtttatttt tacttgtatt ttgcttttgg 120
 t 121

<210> 135
 <211> 350

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(350)
<223> n = A,T,C or G

<400> 135
acttanaacc atgcctagca catcagaatc cctcaaagaa catcagtata atcctataacc 60
atancaagtg gtgactgggt aagcgtgcga caaagggtcag ctggcacatt acttgtgtgc 120
aaacttgata cttttgttct aagtaggaac tagtatacag tncctaggan tggtagtcca 180
gggtgcccc caactcctgc agccgctcct ctgtgccagn ccctgnaagg aactttcgct 240
ccacctcaat caagccctgg gccatgctac ctgcaattgg ctgaacaaac gtttgctgag 300
ttcccaagga tgcaaagcct ggtgctcaac tcctggggcg tcaactcagt 350

<210> 136
<211> 399
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(399)
<223> n = A,T,C or G

<400> 136
tgtaccgtga agacgacaga agttgcatgg cagggacagg gcagggccga ggccagggtt 60
gctgtgattg tatccgaata ntccctcgta gaaaagataa tgagatgacg tgagcagcct 120
gcagacttgt gtctgccttc aanaagccag acaggaaggc cctgcctgcc ttggctctga 180
cctggcggcc agccagccag ccacaggtgg gcttcttcct tttgtggtga caacnccaag 240
aaaactgcag aggccagggg tcaggtgtna gtgggtangt gaccataaaa caccaggtgc 300
tcccaggaac ccgggcaaag gccatcccca cctacagcca gcatgcccac tggcgtgatg 360
ggtgcagang gatgaagcag ccagntgttc tgctgtggt 399

<210> 137
<211> 165
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(165)
<223> n = A,T,C or G

<400> 137
actggtgtgg tnggggggtga tgctgggtgg anaagttgan gtgacttcan gatggtgtgt 60
ggaggaagtg tgtgaacgta gggatgtaga ngttttggcc gtgctaaatg agcttcggga 120
ttggctggtc ccactgggtg tcaactgtcat tgggtggggt cctgt 165

<210> 138

```
<220>  
<221> misc_feature  
<222> (1)...(338)  
<223> n = A,T,C or G
```

```
<210> 139
<211> 382
<212> DNA
<213> Homo sapien
```

```
<210> 140
<211> 200
<212> DNA
<213> Homo sapien
```

```
<220>  
<221> misc_feature  
<222> (1)...(200)  
<223> n = A,T,C or G
```

```
<210> 141
<211> 335
<212> DNA
<213> Homo sapien
```

<220>
 <221> misc_feature
 <222> (1)...(335)
 <223> n = A,T,C or G

<400> 141
 actttatttt caaaacactc atatgttgca aaaaacacat agaaaaataa agtttggtgg 60
 ggggtgctgac taaacttcaa gtcacagact tttatgtgac agattggagc aggggttggt 120
 atgcatgtag agaaccctaa ctaattttatt aaacaggata gaaacaggct gtctgggtga 180
 aatggttctg agaaccatcc aattcacctg tcagatgctg atanactagc tcttcagatg 240
 tttttctacc agttcagaga tnggttaatg actanttcca atgggggaaaa agcaagatgg 300
 attcacaaac caagtaattt taaacaaaga cactt 335

<210> 142
 <211> 459
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(459)
 <223> n = A,T,C or G

<400> 142
 accagggttaa tattgccaca tatatccttt ccaattgcgg gctaaacaga cgtgtattta 60
 gggttgttta aagacaacct agcttaatat caagagaaat tgtgacctt catggagtat 120
 ctgatggaga aaacactgag ttttgacaaa tcttatttta ttcagatagc agtctgatca 180
 cacatggtcc aacaacactc aaataataaa tcaaataatna tcagatgtta aagattggtc 240
 ttcaaacatc atagccaatg atgccccgct tgcctataat ctctccgaca taaaaccaca 300
 tcaaacacctc agtggccacc aaaccattca gcacagcttc cttaactgtg agctgtttga 360
 agctaccagt ctgagcacta ttgactatnt ttttcangct ctgaatagct ctagggatct 420
 cagcangggg gggaggaacc agctcaacct tggcgtant 459

<210> 143
 <211> 140
 <212> DNA
 <213> Homo sapien

<400> 143
 acatttcctt ccaccaagtc aggactcctg gcttctgtgg gagttcttat cacctgaggg 60
 aaatccaaac agtctctcct agaaaggaat agtgtcacca accccaccca tctccctgag 120
 accatccgac ttccctgtgt 140

<210> 144
 <211> 164
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature

cacttaaattg tggtcagtgt ttggacttgt taactantgg catctttggg t 111

<210> 151
 <211> 196
 <212> DNA
 <213> Homo sapien

<400> 151
 agcgcggcag gtcattattga acattccaga tacctatcat tactcgatgc tgttgataac 60
 agcaagatgg ctttgaactc agggtcacca ccagctattg gaccttacta tgaaaaccat 120
 ggataccaac cggaaaaccc ctatcccgca cagcccactg tggccccac tgtctacgag 180
 gtgcatccgg ctccagt 196

<210> 152
 <211> 132
 <212> DNA
 <213> Homo sapien

<400> 152
 acagcacttt cacatgtaag aaggagagaaa ttcttaaattg taggagaaag ataacagAAC 60
 cttcccccttt tcatctagtgt gtggaaacct gatgctttat gttgacagga atagaaccag 120
 gagggagtgt gt 132

<210> 153
 <211> 285
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(285)
 <223> n = A,T,C or G

<400> 153
 acaanaccca nganaggcca ctggccgtgg tgtcatggcc tccaaacatg aaagtgtcag 60
 cttctgctct tatgtcctca tctgacaact ctttaccatt tttatcctcg ctcagcagga 120
 gcacatcaat aaagtccaaa gtcttggact tggccttggc ttggaggaag tcatcaacac 180
 cctggctagt gaggggtgcgg cgccgctcct ggatgacggc atctgtgaag tcgtgcacca 240
 gtctgcaggc cctgtggaag cgccgtccac acggagtnag gaatt 285

<210> 154
 <211> 333
 <212> DNA
 <213> Homo sapien

<400> 154
 accacagtcc tgttggggcca gggcttcatg accctttctg tgaaaagcca tattatcacc 60
 accccaaatt tttccttaaa tatctttaac tgaaggggtc agcctcttga ctgcaaagac 120
 cctaagccgg ttacacagct aactcccact ggccttgatt tgtgaaattg ctgctgcctg 180
 attggcacag gagtgaagg tgttcagctc cctcctccg tggaacgaga ctctgatttg 240
 agtttcacaa attctcgggc cacctcgtca ttgctcctct gaaataaaat ccggagaatg 300

gtcaggcctg tctcatccat atggatcttc cgg

333

<210> 155
 <211> 308
 <212> DNA
 <213> Homo sapien

 <220>
 <221> misc_feature
 <222> (1) ... (308)
 <223> n = A,T,C or G

<400> 155
 actggaaata ataaaaccca catcacagtg ttgtgtcaaa gatcatcagg gcatggatgg 60
 gaaagtgctt tgggaactgt aaagtgccta acacatgac gatgattttt gttataatat 120
 ttgaatcacg gtgcatacaa actctcctgc ctgctcctcc tgggccccag cccagcccc 180
 atcacagctc actgctctgt tcatccaggc ccagcatgta gtggctgatt cttcttggct 240
 gcttttagcc tccanaagtt tctctgaagc caaccaaacc tctangtgta aggcattgctg 300
 gccctggt 308

<210> 156
 <211> 295
 <212> DNA
 <213> Homo sapien

<400> 156
 accttgctcg gtgcttggaa catattagga actcaaaata tgagatgata acagtgccta 60
 ttattgatta ctgagagAAC tgtagacat ttagttgaag attttctaca caggaaactga 120
 gaataggaga ttatgttttg cctcatatt ctctcctatc ctcttgcct cattctatgt 180
 ctaatatatt ctcaatcaaa taagggttagc ataatcagga aatcgaccaa ataccaatat 240
 aaaaccagat gtctatcctt aagattttca aatagaaaac aaattaacag actat 295

<210> 157
 <211> 126
 <212> DNA
 <213> Homo sapien

<400> 157
 acaagttaa atagtgtgt cactgtgcat gtgctgaaat gtgaaatcca ccacatttct 60
 gaagagcaaa acaaattctg tcatgtaatc tctatcttgg gtcgtgggta tatctgtccc 120
 cttagt 126

<210> 158
 <211> 442
 <212> DNA
 <213> Homo sapien

 <220>
 <221> misc_feature
 <222> (1) ... (442)
 <223> n = A,T,C or G

<400> 158

```

accactggt cttggaacac cccatcctta atacgatgat ttttctgtcg tgtgaaaatg      60
aanccagcag gctgccccta gtcagtcctt ccttcagag aaaaagagat ttgagaaagt      120
gcctgggtaa ttcaccatta atttcctccc ccaaactctc tgagtcttcc cttaatatgt      180
ctggtggttc tgaccaaagc aggtcatggt ttgttgagca tttgggatcc cagtgaagta      240
natgtttgta gccttgcata cttagccctt cccacgcaca aacggagtgg cagagtgggtg      300
ccaaccctgt tttcccagtc cacgtagaca gattcacagt gcggaattct ggaagctgga      360
nacagacggg ctctttgcag agccgggact ctgagangga catgagggcc tctgcctctg      420
tgttcattct ctgatgtcct gt                                     442

```

<210> 159

<211> 498

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(498)

<223> n = A,T,C or G

<400> 159

```

acttccaggt aacgttggtg tttccgttga gcctgaactg atgggtgacg ttgtagggtc      60
tccaacaaga actgaggttg cagagcgggt agggaagagt gctgttccag ttgcacctgg      120
gctgctgtgg actgttggtg attcctcact acggcccaag gttgtggaac tggcanaaaag      180
gtgtgttggt gganttgagc tcgggcgggt gtggtagggt gtgggctctt caacaggggc      240
tgctgtggtg ccgggangtg aangtggtgt gtcacttgag cttggccagc tctggaaagt      300
antanattct tcctgaaggc cagcgttgtt ggagctggca ngggtcantg ttgtgtgtaa      360
cgaaccagtg ctgctgtggg tgggtgtana tcctccacaa agcctgaagt tatggtgtcn      420
tcaggttaana atgtggtttc agtgtccctg ggcngctgtg gaaggttgta nattgtcacc      480
aagggaataa gctgtggt                                     498

```

<210> 160

<211> 380

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(380)

<223> n = A,T,C or G

<400> 160

```

acctgcatcc agcttcccctg ccaaactcac aaggagacat caacctctag acagggaaac      60
agcttcagga tacttccagg agacagagcc accagcagca aaacaaatat tcccatgcct      120
ggagcatggc atagaggaag ctganaaatg tggggctctga ggaagccatt tgagtctggc      180
cactagacat ctcatcagcc acttgtgtga agagatgcc ccatgaccca gatgcctctc      240
ccacccttac ctccatctca cacacttgag ctttccactc tgtataattc taacatcctg      300
gagaaaaatg gcagtttgac cgaacctgtt cacaacggta gaggctgatt tctaacgaaa      360
cttgtagaat gaagcctgga                                     380

```


tatanccata cacagagcca actctcaggg caaggcnatg gttggggcag anccagagac 180
tcaatctgan tccaaagtgg tggctggaac actgggtcatg acanaggcag tgactctgac 240
tganctc 247

<210> 168
<211> 273
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(273)
<223> n = A,T,C or G

<400> 168
acttctaagt tttctagaag tggaaggatt gtantcatcc tgaaaatggg tttacttcaa 60
aatccctcan ccttgttctt cacnactgtc tatactgana gtgtcatgtt tccacaaagg 120
gctgacacct gagcctgnat tttcactcat ccctgagaag ccctttccag tagggtgggc 180
aattcccaac ttccttgcca caagcttccc aggctttctc ccctggaaaa ctccagcttg 240
agtcccagat acactcatgg gctgccttg gca 273

<210> 169
<211> 431
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(431)
<223> n = A,T,C or G

<400> 169
acagccttgg cttccccaaa ctccacagtc tcagtgcaga aagatcatct tccagcagtc 60
agctcagacc aggggtcaaag gatgtgacat caacagtttc tggtttcaga acaggttcta 120
ctactgtcaa atgaccccc atacttcctc aaaggctgtg gtaagttttg cacagggtgag 180
ggcagcagaa aggggggtant tactgatgga caccatcttc tctgtatact ccacactgac 240
cttgccatgg gcaaaggccc ctaccacaaa aacaatagga tcaactgctgg gcaccagctc 300
acgcacatca ctgacaaccg ggatggaaaa agaantgcc aactttcatac atccaactgg 360
aaagtgatct gatactggat tcttaattac cttcaaaagc ttctgggggc catcagctgc 420
tcgaacactg a 431

<210> 170
<211> 266
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(266)
<223> n = A,T,C or G

Met Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro
 1 5 10 15
 Leu Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser
 20 25 30
 Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr
 35 40 45
 Ala Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly
 50 55 60
 Arg Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu
 65 70 75 80
 Glu Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe
 85 90 95
 Cys Ala Gly Gly Gly Gln Xaa Gln Xaa Asp Ser Cys Asn Gly Asp Ser
 100 105 110
 Gly Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe
 115 120 125
 Gly Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn
 130 135 140
 Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
 145 150 155

<210> 173

<211> 1265

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(1265)

<223> n = A,T,C or G

<400> 173

ggcagcccg	actgcagcc	ctggcaggcg	gcactgggtca	tggaaaacga	attgttctgc	60
tcgggctcc	tgggtcatcc	gcagtgggtg	ctgtcagccg	cacactgttt	ccagaactcc	120
tacaccatcg	ggctgggcct	gcacagtctt	gagggccgacc	aagagccagg	gagccagatg	180
gtggaggcca	gcctctccgt	acggcaccga	gagtacaaca	gacccttgct	cgctaacgac	240
ctcatgtctca	tcaagttgga	cgaatccgtg	tccgagtctg	acaccatccg	gagcatcagc	300
attgcttcgc	agtgccttac	cgcggggaac	tcttgccctg	tttctggctg	gggtctgctg	360
gcgaacggtg	agctcacggg	tgtgtgtctg	ccctcttcaa	ggaggtcctc	tgcccagtcg	420
cgggggctga	cccagagctc	tgcgtcccag	gcagaatgcc	taccgtgctg	cagtgcgtga	480
acgtgtcggg	ggtgtctgag	gaggtctgca	gtaagctcta	tgaccgctg	taccaccca	540
gcatgttctg	cgccggcgga	gggcaagacc	agaaggactc	ctgcaacggg	gactctgggg	600
ggccccctgat	ctgcaacggg	tacttgccag	gccttggtgc	tttcggaaaa	gccccgtgtg	660
gccaagttgg	cgtgccaggt	gtctacacca	acctctgcaa	attcactgag	tggatagaga	720
aaaccgtcca	ggccagttaa	ctctggggac	tgggaaccca	tgaaattgac	ccccaaatac	780
atcctgcgga	aggaattcag	gaatatctgt	tcccagcccc	tcctccctca	ggcccaggag	840
tccaggcccc	cagcccctcc	tccctcaaac	caagggtaca	gatccccagc	ccctccctcc	900
tcagaccag	gagtccagac	ccccagcccc	ctcctccctc	agaccagga	gtccagcccc	960
tcctccntca	gaccaggag	tccagacccc	ccagccctc	ctccctcaga	cccaggggtt	1020
gaggccccca	acccctcctc	cttcagagtc	agagggtocaa	gcccccaacc	cctcggtccc	1080
cagaccagga	ggttnnagtc	ccagccccctc	tccntcaga	cccagnggtc	caatgccacc	1140

```

tagattttcc ctgnacacag tgcccccttg tggngangttg acccaacctt accagttggt      1200
ttttcatttt tngtcccttt cccttagatc cagaaataaa gtttaagaga ngngcaaaaa      1260
aaaaa                                                                    1265

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```

<210> 174
<211> 1459
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(1459)
<223> n = A,T,C or G

```

```

<400> 174
ggtcagccgc acactgtttc cagaagtgag tgcagagctc ctacaccatc gggctggggcc      60
tgcacagtct tgaggccgac caagagccag ggagccagat ggtggaggcc agcctctccg      120
tacggcaccc agagtacaac agacccttgc tcgctaacga cctcatgctc atcaagttgg      180
acgaatccgt gtccgagtct gacaccatcc ggagcatcag cattgcttcg cagtgcctta      240
ccgcggggaa ctcttgccct gtttctggct ggggtctgct ggcgaacggt gagctcacgg      300
gtgtgtgtct gccctcttca aggaggtcct ctgccagtc gcgggggctg acccagagct      360
ctgctgctcca ggcagaatgc ctaccgtgct gcagtgcgtg aacgtgtcgg tgggtgtctga      420
ngaggtctgc antaagctct atgaccgct gtaccacccc ancatgttct gcgccggcgg      480
agggcaagac cagaaggact cctgcaacgt gagagagggg aaaggggagg gcaggcgact      540
caggggaagg tggagaaggg ggagacagag acacacaggg ccgcatggcg agatgcagag      600
atggagagac acacagggag acagtgacaa ctagagagag aaactgagag aaacagagaa      660
ataaacacag gaataaagag aagcaaagga agagagaaac agaaacagac atggggaggc      720
agaaacacac acacatagaa atgcagttga ccttccaaca gcatggggcc tgagggcggt      780
gacctccacc caatagaaaa tcctcttata acttttgact ccccaaaaac ctgactagaa      840
atagcctact gttgacgggg agccttacca ataacataaa tagtcgattt atgcatacgt      900
tttatgcatt catgatatac ctttggttga attttttgat atttctaagc tacacagttc      960
gtctgtgaat ttttttaa atgttgcaact ctccataaat ttttctgatg tgtttattga     1020
aaaaatccaa gtataagtgg acttgatgc tcaaaccagg gttgttcaag ggtcaactgt     1080
gtaccagag ggaacagtg acacagattc atagaggtga aacacgaaga gaaacaggaa     1140
aatcaagac tctacaaaga ggctgggcag ggtggctcat gcctgtaatc ccagcacttt     1200
gggaggcgag gcaggcagat cacttgagggt aaggagttca agaccagcct ggccaaaatg     1260
gtgaaatcct gtctgtacta aaaatacaaa agttagctgg atatggtggc aggcgcctgt     1320
aatcccagct acttgggagg ctgaggcagg agaattgctt gaatatggga ggcagagggt     1380
gaagtgagtt gagatcacac cactatactc cagctggggc aacagagtaa gactctgtct     1440
caaaaaaaaa aaaaaaaaaa                                                                    1459

```

```

<210> 175
<211> 1167
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(1167)
<223> n = A,T,C or G

```

<400> 175

```

gcgcagccct ggccaggcgc actgggtcatg gaaaacgaat tgtttctgctc gggcgctcctg      60
gtgcacccgc agtgggtgct gtcagccgca cactgtttcc agaactccta caccatcggg      120
ctgggcctgc acagtcttga ggccgaccaa gagccaggga gccagatggt ggaggccagc      180
ctctccgtac ggcacccaga gtacaacaga ctcttgctcg ctaacgacct catgtctatc      240
aagttggacg aatccgtgtc cgagtctgac accatccgga gcatcagcat tgcttcgcag      300
tgccctaccg cggggaactc ttgcctcgtn tctggctggg gtctgctggc gaacggcaga      360
atgcctaccg tgctgcactg cgtgaacgtg tgggtggtgt ctgaggangt ctgcagtaag      420
ctctatgacc cgctgtacca ccccagcatg ttctgcgccg gcggaggggca agaccagaag      480
gactcctgca acggtgactc tggggggccc ctgatctgca acgggtactt gcagggcctt      540
gtgtctttcg gaaaagcccc gtgtggccaa cttggcgtgc cagggtgtcta caccaacctc      600
tgcaaattca ctgagtggat agagaaaacc gtccagncca gttaactctg gggactggga      660
acccatgaaa ttgaccccca aatacatcct gcggaangaa ttcaggaata tctgttccca      720
gcccctcctc cctcaggccc aggagtccag gcccacagcc cctcctccct caaaccaagg      780
gtacagatcc ccagccctc ctccctcaga cccaggagtc cagacccccc agcccctcnt      840
ccntcagacc caggagtcca gcccctcctc cntcagacgc aggagtccag acccccagc      900
ccntcntccg tcagaccagc ggggtgcaggc ccccaacccc tcntcntca gagtcagagg      960
tccaagcccc caaccctcgt ttccccagac ccagaggtnc aggtcccagc cctcctccc      1020
tcagaccagc cgggtccaatg ccacctagan tntccctgta cacagtgcc ccttggtggca      1080
ngttgacca accttaccag ttgggttttc attttttgtc cctttccctt agatccagaa      1140
ataaagtnta agagaagcgc aaaaaaa      1167

```

<210> 176

<211> 205

<212> PRT

<213> Homo sapien

<220>

<221> VARIANT

<222> (1)...(205)

<223> Xaa = Any Amino Acid

<400> 176

```

Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp
 1              5              10              15
Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu
      20              25              30
Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val
      35              40              45
Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Leu Leu Leu
      50              55              60
Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser
65              70              75              80
Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly
      85              90              95
Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met
      100             105             110
Pro Thr Val Leu His Cys Val Asn Val Ser Val Val Ser Glu Xaa Val
      115             120             125
Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala
      130             135             140

```

002230-002230

```
<210> 177
<211> 1119
<212> DNA
<213> Homo sapien
```

```
<210> 178
<211> 164
<212> PRT
<213> Homo sapien
```

```
<220>  
<221> VARIANT  
<222> (1)...(164)  
<223> Xaa = Any Amino Acid
```

<400> 178															
Met	Glu	Asn	Glu	Leu	Phe	Cys	Ser	Gly	Val	Leu	Val	His	Pro	Gln	Trp
1				5					10					15	
Val	Leu	Ser	Ala	Ala	His	Cys	Phe	Gln	Asn	Ser	Tyr	Thr	Ile	Gly	Leu
			20					25					30		
Gly	Leu	His	Ser	Leu	Glu	Ala	Asp	Gln	Glu	Pro	Gly	Ser	Gln	Met	Val

```

      35              40              45
Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu Leu
  50              55              60
Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser
  65              70              75              80
Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly
      85              90              95
Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Asp Ala Val
      100             105             110
Ile Ala Ile Gln Ser Xaa Thr Val Gly Gly Trp Glu Cys Glu Lys Leu
      115             120             125
Ser Gln Pro Trp Gln Gly Cys Thr Ile Ser Ala Thr Ser Ser Ala Arg
      130             135             140
Thr Ser Cys Cys Ile Leu Thr Gly Cys Ser Leu Leu Leu Thr Ala Ser
  145             150             155             160
Pro Gly Thr Leu

```

```

<210> 179
<211> 250
<212> DNA
<213> Homo sapien

```

```

<400> 179
ctggagtgcc ttggtgtttc aagcccctgc aggaagcaga atgcaccttc tgaggcacct      60
ccagctgccc ccggccgggg gatgcgaggc tcggagcacc cttgcccggc tgtgattgct      120
gccaggcact gttcatctca gcttttctgt ccctttgctc ccggcaagcg cttctgctga      180
aagttcatat ctggagcctg atgtcttaac gaataaaggt cccatgctcc acccgaaaaa      240
aaaaaaaaaa                                     250

```

```

<210> 180
<211> 202
<212> DNA
<213> Homo sapien

```

```

<400> 180
actagtccag tgtggtggaa ttccattgtg ttgggcccac cacaatggct acctttaaca      60
tcacccagac ccgccccctg cccgtgcccc acgtgctgc taacgacagt atgatgctta      120
ctctgctact cggaaactat ttttatgtaa ttaatgtatg ctttcttggt tataaatgcc      180
tgatttaaaa aaaaaaaaaa aa                                     202

```

```

<210> 181
<211> 558
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(558)
<223> n = A,T,C or G

```

<213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(496)
 <223> n = A,T,C or G

<400> 184
 accgaattgg gaccgctggc ttataagcga tcatgtyynt ccrgtatkac ctcaacgagc 60
 agggagatcg agtctatacg ctgaagaaat ttgacccgat gggacaacag acctgctcag 120
 cccatcctgc tcggttctcc ccagatgaca aatactctsg acaccgaatc accatcaaga 180
 aacgcttcaa ggtgctcatg acccagcaac cgcgccctgt cctctgaggg tcccttaaac 240
 tgatgtcttt tctgccacct gttacccctc ggagactccg taaccaaact ctteggactg 300
 tgagccctga tgcctttttg ccagccatac tctttggcat ccagtctctc gtggcgattg 360
 attatgcttg tgtgaggcaa tcatggtggc atcaccata aagggaacac atttgacttt 420
 tttttctcat attttaaatt actacmagaw tattwmagaw waaatgawtt gaaaaactst 480
 taaaaaaaaa aaaaaa 496

<210> 185
 <211> 384
 <212> DNA
 <213> Homo sapien

<400> 185
 gctggtagcc tatggcgkgg cccacggagg ggctcctgag gccacggrac agtgacttcc 60
 caagtatcyt ggcsgcgtc ttctaccgtc cctacctgca gatcttcggg cagattcccc 120
 aggaggacat ggacgtggcc ctcatggagc acagcaactg ytcgtcggag cccggcttct 180
 gggcacaccc tcctggggcc caggcgggca cctgcgtctc ccagtatgcc aactggcttg 240
 tgggtgctgct cctcgctcatc ttctgctcg tggccaacat cctgctggtc aacttgctca 300
 ttgccatgtt cagttacaca ttccggcaaa tacagggcaa cagcgatctc tactgggaag 360
 gcgcagcgtt accgcctcat ccgg 384

<210> 186
 <211> 577
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(577)
 <223> n = A,T,C or G

<400> 186
 gagttagctc ctccacaacc ttgatgaggt cgtctgcagt ggctctctgc ttcataccgc 60
 tnccatcgtc atactgtagg tttgccacca cytcttgga tcttggggcg gentaatatt 120
 ccaggaaact ctcaatcaag tcaccgtcga tgaaacctgt gggctggttc tgtcttcgc 180
 tcggtgtgaa aggatctccc agaaggagt ctcgatcttc cccacacttt tgatgacttt 240
 attgagtcga ttctgcatgt ccagcaggag gttgtaccag ctctctgaca gtgaggtcac 300
 cagccctatc atgccgttga mcgtgccga garcaccgag ccttgtgtgg gggkkgaagt 360
 ctacccaga ttctgatta ccagagagcc gtggcaaaag acattgacaa actcgcccag 420
 gtggaaaaag amcamctcct ggargtgctn gccgctctc gtcmgttggt ggcagcgctw 480
 tccttttgac acacaaacaa gttaaaggca ttttcagccc ccagaaantt gtcacatcc 540
 aagatntcgc acagcactna tccagttggg attaaat 577

<210> 187
 <211> 534
 <212> DNA
 <213> Homo sapien

 <220>
 <221> misc_feature
 <222> (1)...(534)
 <223> n = A,T,C or G

<400> 187
 aacatcttcc tgtataatgc tgtgtaatat cgatccgatn ttgtctgstg agaatycatw 60
 actkggaaaa gmaacattaa agcctggaca ctgggtattaa aattcacaat atgcaacact 120
 ttaaacagtg tgtcaatctg ctcccyynac tttgtcatca ccagtctggg aakaagggtg 180
 tgccctattc acacctgtta aaagggcgct aagcattttt gattcaacat cttttttttt 240
 gacacaagtc cgaaaaaagc aaaagtaaag agttatyaat ttgttagcca attcactttc 300
 ttcattgggac agagccatyt gatttaaaaa gcaaattgca taatattgag ctttygggagc 360
 tgatatttga gcggaagagt agcctttcta cttcaccaga cacaactccc tttcatattg 420
 ggatgttnac naaagtwatg tctctwacag atgggatgct tttgtggcaa ttctgttctg 480
 aggatctccc agtttattta ccacttgcac aagaaggcgt tttcttcctc aggc 534

<210> 188
 <211> 761
 <212> DNA
 <213> Homo sapien

 <220>
 <221> misc_feature
 <222> (1)...(761)
 <223> n = A,T,C or G

<400> 188
 agaaaccagt atctctnaaa acaacctctc ataccttggt gacctaatth ttgtgtgcgtg 60
 ttgtgtgtgcg cgcataattat atagacaggc acatcttttt tactttttgta aaagcttatg 120
 cctcttttgt atctatatct gtgaaagttt taatgatctg ccataatgtc ttggggacct 180
 ttgtcttctg tgtaaatggt actagagaaa acacctatnt tatgagtcaa tctagttngt 240
 tttattcgac atgaaggaaa tttccagatn acaacactna caaactctcc ctkgackarg 300
 ggggacaaaag aaaagcaaaa ctgamcataa raaacaatwa cctgggtgaga arttgcataa 360
 acagaaatwr ggtagtatat tgaarnacag catcattaaa rmgttwtktt wttctccctt 420
 gcaaaaaaca tgtaacngact tcccgttgag taatgccaag ttgttttttt tatnataaaa 480
 cttgcccttc attacatggt tnaaagtggg gtgggtgggccc aaaatattga aatgatggaa 540
 ctgactgata aagctgtaca aataagcagt gtgcctaaca agcaacacag taatgttgac 600
 atgcttaatt cacaaatgct aatttcatta taaatgtttg ctaaaatata ctttgaacta 660
 tttttctgtn ttcccagagc tgagatntta gattttatgt agtatnaagt gaaaaantac 720
 gaaaaataata acattgaaga aaaananaaa aanaaaaaaa a 761

<210> 189
 <211> 482
 <212> DNA
 <213> Homo sapien


```

cttcctttgt taagacttca tctggtaaag tcttaagttt tgtagaaagg aattyaattg      240
ctcgttctct aacaatgtcc tctccttgaa gtatttggct gaacaacca cctaaagtcc      300
ctttgtgcat ccattttaaa tatacttaat agggcattgk tncactaggt taaattctgc      360
aagagtcatc tgtctgcaaa agttgcgtta gtatatctgc ca                        402

```

```

<210> 192
<211> 601
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(601)
<223> n = A,T,C or G

```

```

<400> 192
gagctcggat ccaataatct ttgtctgagg gcagcacaca tatncagtgc catggnaact      60
ggtctacccc acatgggagc agcatgccgt agntatataa ggtcattccc tgagtcagac      120
atgcytyttt gaytaccgtg tgccaagtgc tgggtgattct yaacacacyt ccatcccggt      180
cttttgtgga aaaactggca cttktctgga actagcarga catcacttac aaattcaccc      240
acgagacact tgaaagggtg aacaaagcga ytccttgcat gctttttgtc cctccggcac      300
cagttgtcaa tactaaccog ctggtttgcc tccatcacat ttgtgatctg tagctctgga      360
tacatctcct gacagtactg aagaacttct tcttttgttt caaaagcacc tcttggtgcc      420
tgttggatca gggtcccatt tcccagtcyg aatgttcaca tggcatattt wacttcccac      480
aaaacattgc gatttgaggc tcagcaacag caaatcctgt tccggcattg gctgcaagag      540
cctcgatgta gccggccagc gccaaaggcag gcgcctgtgag cccaccagc agcagaagca      600
g                                                                601

```

```

<210> 193
<211> 608
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(608)
<223> n = A,T,C or G

```

```

<400> 193
atacagccca natcccacca cgaagatgcg cttgttgact gagaacctga tgcggtcact      60
ggtcccgcgt tagccccagc gactctccac ctgctggaag cggttgatgc tgcactcytt      120
cccaacgcag gcagmagcgg gsccggtcaa tgaactccay tctggtgctg gggtkgacgg      180
tkaagtgcag gaagaggctg accacctcgc ggtccaccag gatgcccagc tgtgcgggac      240
ctgcagcgaa actcctcgat ggatcatgagc ggggaagcgaa tgaggcccag ggccttgccc      300
agaaccttcc gcctgttctc tggcgtcacc tgcagctgct gccgctgaca ctccggcctcg      360
gaccagcgga caaacggcrt tgaacagccg cacctcacgg atgcccagtg tgtcgcgctc      420
caggammgsc accagcgtgt ccagggtcaat gtcgggtgaag ccctccgcgg gtrtgggcgt      480
ctgcagtgtt tttgtcgatg ttctccaggg acaggctggc cagctgcggt tcatcgaaga      540
gtcgcgcctg cgtgagcagc atgaaggcgt tgtcggctcg cagttcttct tcaggaactc      600
cacgcaat                                                                608

```

<210> 194
 <211> 392
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(392)
 <223> n = A,T,C or G

<400> 194
 gaacggctgg accttgccctc gcattgtgct tgctggcagg gaataccttg gcaagcagyt 60
 ccagtccgag cagccccaga ccgctgccgc ccgaagctaa gcctgcctct ggccttcccc 120
 tccgcctcaa tgcagaacca gtagtgggag cactgtgttt agagttaaga gtgaacactg 180
 tttgatttta cttgggaatt tcctctgtta tatagctttt cccaatgcta atttccaaac 240
 aacaacaaca aaataacatg tttgcctgtt aagttgtata aaagtaggtg attctgtatt 300
 taaagaaaat attactgtta catatactgc ttgcaatttc tgtatttatt gktnctstgg 360
 aaataaatat agttattaaa ggttgtcant cc 392

<210> 195
 <211> 502
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(502)
 <223> n = A,T,C or G

<400> 195
 ccsttkgagg ggkagggkyc cagttyccga gtggaagaaa caggccagga gaagtgcgtg 60
 ccgagctgag gcagatgttc ccacagtgac ccccagagcc stgggstata gtytctgacc 120
 cctcncaagg aaagaccacs ttctggggac atgggctgga gggcaggacc tagaggcacc 180
 aaggggaaggc cccattccgg ggstgttccc cgaggaggaa gggaaggggc tctgtgtgcc 240
 ccccasgagg aagaggccct gagtcctggg atcagacacc ccttcacgtg tatccccaca 300
 caaatgcaag ctcaccaagg tcccctctca gtccccttcc stacaccctg amcgccact 360
 gscscacacc caccagagc acgccacccg ccatggggar tgtgctcaag gartcgcnng 420
 gcarcgtgga catctngtcc cagaaggggg cagaatctcc aatagangga ctgarcmstt 480
 gctnanaaaa aaaaaaaaaa aa 502

<210> 196
 <211> 665
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(665)
 <223> n = A,T,C or G

<400> 196

```

ggttacttgg tttcattgcc accacttagt ggatgtcatt tagaaccatt ttgtctgctc      60
cctctggaag ccttgcgag agcggacttt gtaattgttg gagaataact gctgaatttt      120
wagctgtttk gagttgatts gcaccactgc acccacaact tcaatatgaa aacyawttga      180
actwatttat tatcttgtga aaagtataac aatgaaaatt ttgttcatac tgtattkac      240
aagtatgatg aaaagcaawa gatatatatt cttttattat gttaaattat gattgccatt      300
attaatcggc aaaatgtgga gtgtatgttc ttttcacagt aatatatgcc ttttgtaact      360
tcacttgggt attttattgt aaatgartta caaaattctt aatttaagar aatggatgt      420
watatttatt tcattaattt ctttcctkgt ttacgtwaat tttgaaaaga wtgcattgatt      480
tcttgacaga aatcgatctt gatgctgtgg aagtagtttg acccacatcc ctatgagttt      540
ttcttagaat gtataaagggt tgtagcccat cnaacttcaa agaaaaaaat gaccacatac      600
tttgcaatca ggctgaaatg tggcatgctn ttctaattcc aactttataa actagcaaan      660
aagtg                                          665

```

```

<210> 197
<211> 492
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(492)
<223> n = A,T,C or G

```

```

<400> 197
tttntttttt ttttttttgc aggaaggatt ccatttattg tggatgcatt ttcacaatat      60
atgtttattg gagcgatcca ttatcagtga aaagtatcaa gtgtttataa natttttagg      120
aaggcagatt cacagaacat gctngtcngc ttgcagtttt acctcgtana gatnacagag      180
aattatagtc naaccagtaa acnaggaatt tacttttcaa aagattaaat ccaaactgaa      240
caaaattcta ccctgaaact tactccatcc aaatattgga ataanagtca gcagtgatac      300
attctcttct gaacttttaga ttttctagaa aaatatgtaa tagtgatcag gaagagctct      360
tgttcaaaag tacaacnaag caatgttccc ttaccatagg ccttaattca aactttgatc      420
catttcactc ccatcacggg agtcaatgct acctgggaca cttgtatttt gttcatnctg      480
ancntggctt aa                                          492

```

```

<210> 198
<211> 478
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(478)
<223> n = A,T,C or G

```

```

<400> 198
tttnttttgn atttcantct gtannaanta ttttcattat gtttattana aaaatatnaa      60
tgtntccaen acaaatcatn ttacntnagt aagaggccan ctacattgta caacatacac      120
tgagtatatt ttgaaaagga caagttttaa gtanacncat attgccganc atancacatt      180
tatacatggc ttgattgata tttagcacag canaaactga gtgagttacc agaaanaaat      240
natatatgtc aatcngatth aagatacaaa acagatccta tggtaacatan catcntgtag      300
gagttgtggc tttatgttta ctgaaagtca atgcagttcc tgtacaaaga gatggccgta      360

```

```

agcattctag tacctctact ccatgggttaa gaatcgtaca cttatgttta catatgtnca    420
gggtaagaat tgtgttaagt naanttatgg agaggtccan gagaaaaatt tgatncaa      478

```

```

<210> 199
<211> 482
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(482)
<223> n = A,T,C or G

```

```

<400> 199
agtgacttgt cctccaacaa aaccccttga tcaagtttgt ggcactgaca atcagaccta    60
tgctagttcc tgtcatctat tcgctactaa atgcagactg gaggggacca aaaaggggca    120
tcaactccag ctggattatt ttggagcctg caaatctatt cctacttgta cggactttga    180
agtgattcag tttcctctac ggatgagaga ctggctcaag aatatactca tgcagcttta    240
tgaagccnac tctgaacacg ctggttatct nagatgagaa ncagagaaat aaagtcnaga    300
aaatttacct ggangaaaag aggccttngg ctggggacca tccattgaa ccttctctta    360
anggacttta agaanaaaact accacatgtn tgtngtatcc tgggtgccngg ccgtttantg    420
aacntngacn ncacccttnt ggaatanant cttgaengcn tectgaactt gctcctctgc    480
ga                                                                    482

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<210> 200
<211> 270
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(270)
<223> n = A,T,C or G

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<400> 200
cggccgcaag tgcaactcca gctggggcgcg tgcggacgaa gattctgcca gcagttggtc    60
cgactgcgac gacggcggcg gcgacagtcg caggtgcagc gcgggcgcct ggggtcttgc    120
aaggctgagc tgacgccgca gaggtcgtgt cacgtccac gaccttgacg ccgtcgggga    180
cagccggaac agagcccggg gaangcggga ggcctcgggg agcccctcgg gaaggcggcg    240
ccgagagata cgcaggtgca ggtggccgcc
                                                                    270

```

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<210> 201
<211> 419
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(419)
<223> n = A,T,C or G

```

<400> 201

tttttttttt	ttttggaatc	tactgcgagc	acagcaggtc	agcaacaagt	ttattttgca	60
gctagcaagg	taacagggta	gggcatgggt	acatgttcag	gtcaacttcc	tttgtcgtgg	120
ttgattgggt	tgtctttatg	ggggcggggg	ggggtagggg	aaancgaagc	anaantaaca	180
tggagtgggt	gcacctccc	tgtagaacct	ggttacnaaa	gcttggggca	gttcacctgg	240
tctgtgaccg	tcattttctt	gacatcaatg	ttattagaag	tcaggatata	ttttagagag	300
tccactgtnt	ctggagggag	attaggggtt	cttgccaana	tccaancaa	atccacntga	360
aaaagtggga	tgatncangt	acngaatacc	ganggcatan	ttctcatant	cggtggcca	419

<210> 202

<211> 509

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(509)

<223> n = A,T,C or G

<400> 202

tttntttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	60
tggcacttaa	tccattttta	tttcaaaatg	tctacaaant	ttnaatncnc	cattatacng	120
gtnattttnc	aaaatctaaa	nnttattcaa	atntnagcca	aantccttac	ncaaantnaa	180
tacncncaa	aatcaaaaat	atacntntct	ttcagcaaac	ttngttacat	aaattaaana	240
aatatatacg	gctggtgttt	tcaaagtaca	attatcttaa	cactgcaaac	atnttttnaa	300
ggaactaaaa	taaaaaaaa	cactnccgca	aagggttaaag	ggaacaacaa	attcntttta	360
caacancnnc	nattataaaa	atcatatctc	aaatcttagg	ggaatatata	cttcacacng	420
ggatcttaac	ttttactnca	ctttgtttat	ttttttanaa	ccattgtntt	gggcccaaca	480
caatggnaat	nccnccncnc	tggactagt				509

<210> 203

<211> 583

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(583)

<223> n = A,T,C or G

<400> 203

tttttttttt	ttttttttga	ccccctctt	ataaaaaaca	agttaccatt	ttattttact	60
tacacatatt	tattttataa	ttggtattag	atattcaaaa	ggcagctttt	aaaatcaaac	120
taaatggaaa	ctgccttaga	tacataattc	ttaggaatta	gcttaaaatc	tgccataaagt	180
gaaaatcttc	tctagctctt	ttgactgtaa	attttttgact	cttgtaaaac	atccaaattc	240
atttttcttg	tctttaaaat	tatctaattc	ttccattttt	tccctattcc	aagtcaattt	300
gcttctctag	cctcatttcc	tagctcttat	ctactattag	taagtggctt	ttttcctaaa	360
agggaaaaaca	ggaagagana	atggcacaca	aaacaaacat	tttatattca	tatttctacc	420
tacgttaata	aaatagcatt	ttgtgaagcc	agctcaaaaag	aaggcttaga	tccttttatg	480
tccatttttag	tcactaaacg	atatcnaaag	tgccagaatg	caaaagggtt	gtgaacattt	540
attcaaaagc	taatataaga	tatttccat	actcatcttt	ctg		583

<220>
 <221> misc_feature
 <222> (1)...(328)
 <223> n = A,T,C or G

<400> 212
 acccaaaaat ccaatgctga atatttggct tcattattcc canattcttt gattgtcaaa 60
 ggatttaatg ttgtctcagc ttgggcactt cagttaggac ctaaggatgc cagccggcag 120
 gtttatatat gcagcaacaa tattcaagcg cgacaacagg ttattgaact tgcccgccag 180
 ttnaatttca ttcccattga cttgggatcc ttatcatcag ccagagagat tgaaaattta 240
 cccctacnac tctttactct ctgganaggg ccagtgggtg tagctataag cttggccaca 300
 tttttttttc ctttattcct ttgtcaga 328

<210> 213
 <211> 250
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(250)
 <223> n = A,T,C or G

<400> 213
 acttatgagc agagcgacat atccnagtgt agactgaata aaactgaatt ctctccagtt 60
 taaagcattg ctactgaag ggatagaagt gactgccagg agggaaagta agccaaggct 120
 cattatgcca aagganatat acatttcaat tctccaaact tcttcctcat tccaagagtt 180
 ttcaatattt gcatgaacct gctgataanc catgttaana aacaaatata tctctnacct 240
 tctcatcggt 250

<210> 214
 <211> 444
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(444)
 <223> n = A,T,C or G

<400> 214
 acccagaatc caatgctgaa tatttggctt cattattccc agattctttg attgtcaaag 60
 gatttaaatgt tgtctcagct tgggcacttc agttaggacc taaggatgcc agccggcag 120
 tttatatatg cagcaacaat attcaagcgc gacaacaggt tattgaactt gcccgccagt 180
 tgaatttcat tcccattgac ttgggatcct tatcatcagc canagagatt gaaaatttac 240
 ccctacgact ctttactctc tggagagggc cagtgggtgg agctataagc ttggccacat 300
 ttttttttcc tttattcctt tgtcagagat gcgattcatc catatgctan aaaccaacag 360
 agtgactttt acaaaaattcc tataganatt gtgaataaaa ccttacctat agttgccatt 420
 actttgctct ccctaataata cctc 444

<210> 222
 <211> 351
 <212> DNA
 <213> Homo sapien

<400> 222
 agggcgtggt gcggagggcg gtactgacct cattagtagg aggatgcatt ctggcacccc 60
 gttcttcacc tgtcccccaa tccttaaaag gccatactgc ataaagtcaa caacagataa 120
 atgtttgctg aattaaagga tggatgaaaa aaattaataa tgaatttttg cataatccaa 180
 ttttctcttt tatatttcta gaagaagttt ctttgagcct attagatccc gggaatcttt 240
 taggtgagca tgattagaga gcttgtagggt tgctttttaca tatatctggc atatttgagt 300
 ctcgtatcaa aacaatagat tggtaaagggt ggtattattg tattgataag t 351

<210> 223
 <211> 383
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)... (383)
 <223> n = A,T,C or G

<400> 223
 aaaacaaaca aacaaaaaaa acaattcttc attcagaaaa attatcttag ggactgatat 60
 tggtaattat ggtcaattta atwrtrttkt ggggcatttc cttacattgt cttgacaaga 120
 ttaaaatgtc tgtgccaaaa ttttgtattt tatttgagga cttcttatca aaagtaatgc 180
 tgccaaagga agtctaagga attagtagtg tccccmtcac ttgtttggag tgtgctattc 240
 taaaagattt tgatttctctg gaatgacaat tatattttta ctttgggtggg ggaaanagtt 300
 ataggaccac agtcttcact tctgatactt gttaaattaat cttttattgc acttgttttg 360
 accattaagc tatatgttta aaa 383

<210> 224
 <211> 320
 <212> DNA
 <213> Homo sapien

<400> 224
 cccctgaagg cttcttggtta gaaaatagta cagttacaac caataggaac aacaaaaaga 60
 aaaagtttgt gacattgtag tagggagtgt gtacccttca ctcccatca aaaaaaaaaat 120
 ggatacatgg ttaaaggata raagggaat attttatcat atgttctaaa agagaaggaa 180
 gagaaaatac tactttctcr aaatggaagc ccttaaagggt gctttgatac tgaaggacac 240
 aaatgtggcc gtccatcctc ctttaragtt gcatgacttg gacacggtaa ctgttgagcgt 300
 tttaractcm gcattgtgac 320

<210> 225
 <211> 1214
 <212> DNA
 <213> Homo sapien

<400> 225

gaggactgca	gcccgcactc	gcagccctgg	caggcggcac	tggatcatgga	aaacgaattg	60
ttctgctcgg	gcgtcctggg	gcataccgag	tgggtgctgt	cagccgcaca	ctgtttccag	120
aactcctaca	ccatcgggct	gggcctgcac	agtcttgagg	ccgaccaaga	gccagggagc	180
cagatggtgg	agggcagcct	ctccgtacgg	cacccagagt	acaacagacc	cttgctcgtc	240
aacgacctca	tgctcatcaa	gttggacgaa	tcctgtgctg	agtctgacac	catccggagc	300
atcagcattg	cttcgcagtg	ccctaccgcg	gggaactctt	gcctcgtttc	tggctggggg	360
ctgctggcga	acggcagaat	gcctaccgtg	ctgcagtgcg	tgaacgtgtc	ggtggtgtct	420
gaggaggtct	gcagtaagct	ctatgaccgg	ctgtaccacc	ccagcatgtt	ctgcgcgggc	480
ggagggcaag	accagaagga	ctcctgcaac	ggtgactctg	gggggcccct	gatctgcaac	540
gggtacttgc	agggccttgt	gtctttcgga	aaagccccgt	gtggccaagt	tggcgtgcca	600
ggtgtctaca	ccaacctctg	caaattcact	gagtggatag	agaaaaccgt	ccaggccagt	660
taactctggg	gactgggaac	ccatgaaatt	gacccccaaa	tacatcctgc	ggaaggaatt	720
caggaatatc	tgttcccagc	ccctcctccc	tcaggccccag	gagtccaggc	ccccagcccc	780
tcctccctca	aaccaagggt	acagatcccc	agccccctct	ccctcagacc	caggagtcca	840
gacccccccag	ccccctcctc	ctcagaccca	ggagtccagc	ccctcctccc	tcagaccagc	900
gagtccagac	ccccagcccc	ctcctccctc	agaccagggg	gtccaggccc	ccaacccctc	960
ctccctcaga	ctcagaggtc	caagccccca	acccctcctt	ccccagaccc	agaggtccag	1020
gtcccagccc	ctcctccctc	agaccagcgg	gtccaatgcc	acctagactc	tcctgttaca	1080
cagtgcctcc	ttgtggcagc	ttgacccaac	cttaccagtt	ggtttttcat	tttttgtccc	1140
tttcccttag	atccagaaat	aaagtctaag	agaagcgcaa	aaaaaaaaaa	aaaaaaaaaa	1200
aaaaaaaaaa	aaaa					1214

<210> 226

<211> 119

<212> DNA

<213> Homo sapien

<400> 226

accagtatg	tgacgggaga	cggaaccccc	tgtgacagcc	cactccacca	gggttcccaa	60
agaacctggc	ccagtcataa	tcattcatcc	tgacagtggc	aataatcacg	ataaccagt	119

<210> 227

<211> 818

<212> DNA

<213> Homo sapien

<400> 227

acaattcata	gggacgacca	atgaggacag	ggaatgaacc	cggctctccc	ccagccctga	60
tttttgctac	atatgggggc	ccttttcatt	ctttgcaaaa	acactggggt	ttctgagaac	120
acggacggtt	cttagcacia	tttgtgaaat	ctgtgtaraa	ccgggctttg	caggggagat	180
aattttcctc	ctctggagga	aagggtggtg	ttgacaggca	gggagacagt	gacaaggcta	240
gagaaagcca	cgctcggcct	tctctgaacc	aggatggaac	ggcagacccc	tgaaaacgaa	300
gcttgtcccc	ttccaatcag	ccacttctga	gaacccccat	ctaacttcct	actggaaaag	360
agggcctcct	caggagcagt	ccaagagttt	tcaaagataa	cgtgacaact	accatctaga	420
ggaaagggtg	caccctcagc	agagaagccg	agagcttaac	tctggctcgt	tccagagaca	480
acctgctggc	tgtcttgagg	tgcgcccagc	ctttgagagg	ccactacccc	atgaacttct	540
gccatccact	ggacatgaag	ctgaggacac	tgggcttcaa	cactgagttg	tcatgagagg	600
gacaggctct	gccctcaagc	cggctgaggg	cagcaaccac	tctcctcccc	tttctcacgc	660
aaagccattc	ccacaaatcc	agaccatacc	atgaagcaac	gagacccaaa	cagtttggct	720
caagaggata	tgaggactgt	ctcagcctgg	ctttgggctg	acaccatgca	cacacacaag	780
gtccacttct	agggttttcag	cctagatggg	agtcgtgt			818

<210> 228
 <211> 744
 <212> DNA
 <213> Homo sapien

<400> 228
 actggagaca ctgttgaact tgatcaagac ccagaccacc ccaggtctcc ttcgtgggat 60
 gtcattgacgt ttgacatacc tttggaacga gcctcctcct tggaagatgg aagaccgtgt 120
 tcgtggccga cctggcctct cctggcctgt ttcttaagat gcggagtcac atttcaatgg 180
 taggaaaagt ggcttcgtaa aatagaagag cagtcactgt ggaactacca aatggcgaga 240
 tgctcgtgtc acattggggg gctttgggat aaaagattta tgagccaact attctctggc 300
 accagattct aggccagttt gttccactga agcttttccc acagcagtcc acctctgcag 360
 gctggcagct gaatggcctt cgggtggctc tgtggcaaga tcacactgag atcgatgggt 420
 gagaaggcta ggatgcttgt ctagtgcttct tagctgtcac gttggctcct tccaggttgg 480
 ccagacggtg ttggccactc ccttctaaaa cacaggcgcc ctcttggtga cagtgacctg 540
 ccgtggtatg ccttggccca ttccagcagt cccagttatg catttcaagt ttgggggttg 600
 ttcttttcgt taatgttctt ctgtgttggt agctgtcttc atttcctggg ctaagcagca 660
 ttgggagatg tggaccagag atccactcct taagaaccag tggcgaaaga cactttcttt 720
 cttcactctg aagtagctgg tggt 744

<210> 229
 <211> 300
 <212> DNA
 <213> Homo sapien

<400> 229
 cgagtctggg ttttgtctat aaagtttgat ccctcctttt ctcatccaaa tcatgtgaac 60
 cattacacat cgaaataaaa gaaaggtggc agacttgccc aacgccaggc tgacatgtgc 120
 tgcaggggtg ttgtttttta attattattg ttagaaacgt caccacagc ccctgttaat 180
 ttgtatgtga cagccaactc tgagaagggt ctatttttcc acctgcagag gatccagtct 240
 cactaggctc ctcttgccc tcacactgga gtctccgcca gtgtgggtgc ccactgacat 300

<210> 230
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 230
 cagcagaaca aatacaata tgaagagtgc aaagatctca taaaatctat gctgaggaat 60
 gagcgacagt tcaaggagga gaagcttgca gagcagctca agcaagctga ggagctcagg 120
 caatataaag tcctggttca cactcaggaa cgagagctga cccagttaag ggagaagtgt 180
 cggaaggga gagatgcctc cctctcattg aatgagcatc tccaggccct cctcactccg 240
 gatgaaccgg acaagtccca ggggcaggac ctccaagaaa cagacctcgg ccgcgaccac 300
 g 301

<210> 231
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 231

gcaagcacgc	tggcaaactct	ctgtcagggtc	agctccagag	aagccattag	tcatttttagc	60
caggaactcc	aagtccacat	ccttggcaac	tggggacttg	cgcaggttag	ccttgaggat	120
ggcaacacgg	gactttctcat	caggaagtgg	gatgtagatg	agctgatcaa	gacggccagg	180
tctgaggatg	gcaggatcaa	tgatgtcagg	cgggttggtg	ccgccaatga	tgaacacatt	240
tttttttggtg	gacatgccat	ccattttctgt	caggatctgg	ttgatgactc	ggtcagcagc	300
c						301

<210> 232

<211> 301

<212> DNA

<213> Homo sapien

<400> 232

agtaggtatt	tcgtgagaag	ttcaacacca	aaactggaac	atagttctcc	ttcaagtgtt	60
ggcgacagcg	gggttcctg	attctggaat	ataactttgt	gtaaattaac	agccacctat	120
agaagagtcc	atctgtctgtg	aaggagagac	agagaactct	gggttcctgc	gtcctgtcca	180
cgtgctgtac	caagtgtctgg	tgccagcctg	ttacctgttc	tactgaaaa	tctggctaata	240
gctcttgtgt	atcacttctg	attctgacaa	tcaatcaatc	aatggcctag	agcactgact	300
g						301

<210> 233

<211> 301

<212> DNA

<213> Homo sapien

<400> 233

atgactgact	tcccagtaag	gctctctaag	gggtaagtag	gaggatccac	aggatttgag	60
atgctaaggc	cccagagatc	gtttgatcca	accctcttat	tttcagaggg	gaaaatgggg	120
cctagaagtt	acagagcatc	tagctggtgc	gctggcacc	ctggcctcac	acagactccc	180
gagtagctgg	gactacaggc	acacagtcac	tgaagcaggc	cctgttagca	attctatgcg	240
tacaaattaa	catgagatga	gtagagactt	tattgagaaa	gcaagagaaa	atcctatcaa	300
c						301

<210> 234

<211> 301

<212> DNA

<213> Homo sapien

<400> 234

aggtcctaca	catcgagact	catccatgat	tgatatgaat	ttaaaaatta	caagcaaaga	60
cattttattc	atcatgatgc	tttcttttgt	ttcttctttt	cgttttcttc	tttttctttt	120
tcaatttcag	caacatactt	ctcaatttct	tcaggattta	aaatcttgag	ggattgatct	180
cgcctcatga	cagcaagtgc	aatgtttttg	ccacctgact	gaaccacttc	caggagtgcc	240
ttgatcacca	gcttaatggg	cagatcatct	gcttcaatgg	cttcgtcagt	atagttcttc	300
t						301

<210> 235

<211> 283

<212> DNA

<213> Homo sapien

<400> 235

tggtgctgtg	catcaggcgg	gtttgagaaa	tattcaattc	tcagcagaag	ccagaatttg	60
aattccctca	tcttttaggg	aatcatttac	caggtttgga	gaggattcag	acagctcagg	120
tgctttcact	aatgtctctg	aacttctgtc	cctctttgtt	catggatagt	ccaataaata	180
atgttatctt	tgaactgatg	ctcataggag	agaatataag	aactctgagt	gatatcaaca	240
ttagggattc	aaagaaatat	tagatttaag	ctcacactgg	tca		283

<210> 236

<211> 301

<212> DNA

<213> Homo sapien

<400> 236

aggtcctcca	ccaactgcct	gaagcacggg	taaaattggg	aagaagtata	gtgcagcata	60
aatactttta	aatcgatcag	atttccctaa	cccacatgca	atcttcttca	ccagaagagg	120
tcggagcagc	atcattaata	ccaagcagaa	tcggtaatag	ataaatacaa	tggtatatag	180
tggttagacg	gcttcatgag	tacagtgtac	tgtggtatcg	taatctggac	ttgggttgta	240
aagcatcgtg	taccagtcag	aaagcatcaa	tactcgacat	gaacgaatat	aaagaacacc	300
a						301

<210> 237

<211> 301

<212> DNA

<213> Homo sapien

<400> 237

cagtggtagt	ggtgggtggac	gtggcggttg	tcgtgggtgcc	ttttttggtg	cccgtcacaa	60
actcaatttt	tgttcgctcc	tttttggcct	tttccaattt	gtccatctca	attttctggg	120
ccttggctaa	tgctcatag	taggagtcct	cagaccagcc	atggggatca	aacatatcct	180
ttgggtagtt	ggtgcccaagc	tcgtcaatgg	cacagaatgg	atcagcttct	cgtaaatacta	240
gggttccgaa	attctttctt	cctttggata	atgtagttca	tatccattcc	ctcctttatc	300
t						301

<210> 238

<211> 301

<212> DNA

<213> Homo sapien

<400> 238

gggcaggttt	tttttttttt	ttttttgatg	gtgcagaccc	ttgctttatt	tgtctgactt	60
gttcacagtt	cagccccctg	ctcagaaaac	caacgggcca	gctaaggaga	ggaggaggca	120
ccttgagact	tccggagtcg	aggtctctcca	gggttccccca	gcccatcaat	cattttctgc	180
acccctgcc	tgggaagcag	ctccctgggg	ggtgggaatg	ggtgactaga	agggatttca	240
gtgtgggacc	cagggtctgt	tcttcacagt	aggaggtgga	agggatgact	aattttcttta	300
t						301

<210> 239

<211> 239

<212> DNA

<213> Homo sapien

<400> 239

ataagcagct agggaattct ttatttagta atgtcctaac ataaaagtgc acataactgc	60
ttctgtcaaa ccatgatact gagctttgtg acaaccaga aataactaag agaaggcaaa	120
cataatacct tagagatcaa gaaacattta cacagttcaa ctgttttaaaa atagctcaac	180
attcagccag tgagtagagt gtgaatgcc gcatacacag tatacaggtc cttcaggga	239

<210> 240

<211> 300

<212> DNA

<213> Homo sapien

<400> 240

ggtcctaattg aagcagcagc ttccacattt taacgcaggt ttacggtgat actgtccttt	60
gggatctgcc ctccagtga acccttttaag gaagaagtgg gcccaagcta agttccacat	120
gctgggtgag ccagatgact tctgttcctt ggtcactttc ttcaatgggg cgaatggggg	180
ctgccaggtt tttaaaatca tgcttcatct tgaagcacac ggtcacttca ccctcctcac	240
gctgtgggtg tactttgatg aaaataccca ctttgttggc ctttctgaag ctataatgtc	300

<210> 241

<211> 301

<212> DNA

<213> Homo sapien

<400> 241

gaggtctggt gctgaggtct ctgggctagg aagaggagtt ctgtggagct ggaagccaga	60
cctctttgga ggaaactcca gcagctatgt tgggtgtctct gagggaatgc aacaaggctg	120
ctcctccatg tattggaaaa ctgcaaaactg gactcaactg gaaggaagtg ctgctgccag	180
tgtgaagaac cagcctgagg tgacagaaac ggaagcaaac aggaacagcc agtcttttct	240
tcctcctcct gtcatacggg ctctctcaag catcctttgt tgtcaggggc ctaaaaggga	300
g	301

<210> 242

<211> 301

<212> DNA

<213> Homo sapien

<400> 242

ccgaggtcct gggatgcaac caatcactct gtttcacgtg acttttatca ccatacaatt	60
tgtggcattt cctcattttc tacattgtag aatcaagagt gtaaataaat gtatatcgat	120
gtcttcaaga atatatcatt cctttttcac tagaaccat tcaaaatata agtcaagaat	180
cttaatatca acaaatatat caagcaaact ggaaggcaga ataactacca taatttagta	240
taagtaccca aagttttata aatcaaaagc cctaatagata accattttta gaattcaatc	300
a	301

<210> 243

<211> 301

<212> DNA

<213> Homo sapien

<400> 243

```

aggtaagtcc cagtttgaag ctcaaaagat ctggtatgag cataggctca tcgacgacat      60
ggtggcccaa gctatgaaat cagagggagg cttcatcttg gcctgtaaaa actatgatgg      120
tgacgtgcag tcggactctg tggcccaagg gtatggctct ctcggcata gaaccagcgt      180
gctggtttgt ccagatggca agacagtaga agcagaggct gccacggga ctgtaacccg      240
tcactaccgc atgttccaga aaggacagga gacgtccacc aatcccattg cttccatttt      300
t                                                                    301

```

```

<210> 244
<211> 300
<212> DNA
<213> Homo sapien

```

```

<400> 244
gctggtttgc aagaatgaaa tgaatgattc tacagctagg acttaacctt gaaatggaaa      60
gtcatgcaat cccatttgca ggatctgtct gtgcacatgc ctctgtagag agcagcattc      120
ccagggacct tggaaacagt tgacactgta aggtgcttgc tccccagac acatcctaaa      180
aggtgttgta atggtgaaaa cgtcttctct ctttattgcc ctttcttatt tatgtgaaca      240
actgtttgtc ttttgtgtat cttttttaaa ctgtaaagtt caattgtgaa aatgaatatc      300

```

```

<210> 245
<211> 301
<212> DNA
<213> Homo sapien

```

```

<400> 245
gtctgagtat ttaaaatggt attgaaatta tccccacca atgttagaaa agaaagaggt      60
tatatactta gataaaaaat gaggtgaatt actatccatt gaaatcatgc tcttagaatt      120
aaggccagga gatattgtca ttaatgtara cttcaggaca ctagagtata gcagccctat      180
gttttcaaag agcagagatg caattaaata ttgttttagca tcaaaaaggc cactcaatac      240
agctaataaa atgaaagacc taatttctaa agcaattctt tataatttac aaagttttaa      300
g                                                                    301

```

```

<210> 246
<211> 301
<212> DNA
<213> Homo sapien

```

```

<400> 246
ggtctgtcct acaatgcctg cttcttgaaa gaagtcggca ctttctagaa tagctaaata      60
acctgggctt atttttaaaga actatttgta gctcagattg gttttcctat ggctaaaata      120
agtgttctt gtgaaaatta aataaaacag ttaattcaaa gccttgatat atgttaccac      180
taacaatcat actaaatata ttttgaagta caaagtttga catgctctaa agtgacaacc      240
caaattgtgc ttacaaaaca cgttcttaac aaggatgct ttacactacc aatgcagaaa      300
c                                                                    301

```

```

<210> 247
<211> 301
<212> DNA
<213> Homo sapien

```

```

<400> 247

```

```

aggtcctttg gcagggctca tggatcagag ctcaaactgg agggaaaggc atttcgggta      60
gcctaagagg gcgactggcg gcagcacaac caaggaaggc aagggtgttt cccccacgct      120
gtgtcctgtg ttcaggtgcg acacacaatc ctcatgggaa caggatcacc catgcgctgc      180
ccttgatgat caaggttggg gcttaagtgg attaagggag gcaagttctg gggtccttgc      240
cttttcaaac catgaagtca ggctctgtat ccctcctttt cctaactgat attctaacta      300
a                                                                                   301

```

```

<210> 248
<211> 301
<212> DNA
<213> Homo sapien

```

```

<400> 248
aggtccttgg agatgccatt tcagccgaag gactcttctw ttcggaagta caccctcact      60
attaggaaga ttcttagggg taatttttct gaggaaggag aactagccaa cttagaatt      120
acaggaagaa agtggtttgg aagacagcca aagaaataaa agcagattaa attgtatcag      180
gtacattcca gcctgttggc aactccataa aaacatttca gattttaatc ccgaatttag      240
ctaattgagac tggatttttg ttttttatgt tgtgtgtcgc agagctaaaa actcagttcc      300
c                                                                                   301

```

```

<210> 249
<211> 301
<212> DNA
<213> Homo sapien

```

```

<400> 249
gtccagagga agcacctggg gctgaactag gcttgccctg ctgtgaactt gcacttggag      60
ccctgacgct gctgttctcc ccgaaaaacc cgaccgacct ccgcgatctc cgtcccgcgc      120
ccagggagac acagcagtga ctcagagctg gtgcgcacct gtgcctccct cctcaccgcc      180
catcgtaatg aattattttg aaaattaatt ccaccatcct ttcagattct ggatggaaag      240
actgaatctt tgactcagaa ttgtttgctg aaaagaatga tgtgactttc ttagtcattt      300
a                                                                                   301

```

```

<210> 250
<211> 301
<212> DNA
<213> Homo sapien

```

```

<400> 250
ggctctgtgac aaggacttgc aggctgtggg aggcaagtga cccttaacac tacacttctc      60
cttatcttta ttggcttgat aaacataatt atttctaaca ctagcttatt tccagttgcc      120
cataagcaca tcagtacttt tctctggctg gaatagtaaa ctaaagtatg gtacatctac      180
ctaaaagact actatgtgga ataatacata ctaatgaagt attacatgat ttaaagacta      240
caataaaacc aaacatgctt ataacattaa gaaaaacaat aaagatacat gattgaaacc      300
a                                                                                   301

```

```

<210> 251
<211> 301
<212> DNA
<213> Homo sapien

```

<400> 251

```

gccgaggtcc tacatattggc ccagtttccc cctgcatacct ctccagggcc cctgcctcat      60
agacaacctc atagagcata ggagaactgg ttgccctggg ggcaggggga ctgtctggat      120
ggcaggggtc ctcaaaaatg ccactgtcac tgccaggaaa tgcttctgag cagtacacct      180
cattgggatc aatgaaaagc ttcaagaaat cttcaggctc actctcttga aggcccggaa      240
cctctggagg ggggcagtgg aatcccagct ccaggacgga tcctgtcgaa aagatatcct      300
c                                                                                   301

```

<210> 252

<211> 301

<212> DNA

<213> Homo sapien

<400> 252

```

gcaaccaatc actctgtttc acgtgacttt tatcaccata caatttgtgg catttcctca      60
ttttctacat tgtagaatca agagtgtaaa taaatgtata tcgatgtctt caagaatata      120
tcattccttt ttcactagga acccattcaa aatataagtc aagaatctta atatcaacaa      180
atatatcaag caaactggaa ggcagaataa ctaccataat ttagtataag taccctaaagt      240
tttataaatc aaaagcccta atgataacca tttttagaat tcaatcatca ctgtagaatc      300
a                                                                                   301

```

<210> 253

<211> 301

<212> DNA

<213> Homo sapien

<400> 253

```

ttccctaaga agatgttatt ttgttgggtt ttgttcccc tccatctcga ttctcgtacc      60
caactaaaaa aaaaaaataa agaaaaaatg tgctgcgttc tgaaaaataa ctccttagct      120
tggtctgatt gttttcagac cttaaaatat aaacttgttt cacaagcttt aatccatgtg      180
gatttttttt cttagagaac cacaaaacat aaaaggagca agtcggactg aatacctgtt      240
tccatagtgc ccacagggtg ttctctcatat tttctccata ggaaaatgct ttttcccaag      300
g                                                                                   301

```

<210> 254

<211> 301

<212> DNA

<213> Homo sapien

<400> 254

```

cgctgcgcct ttcccttggg ggagggggcaa ggccagaggg ggtccaagtg cagcacgagg      60
aacttgacca attcccttga agcgggtggg ttaaaccctg taaatgggaa caaatcccc      120
ccaaatctct tcatcttacc ctggtggact cctgactgta gaattttttg gttgaaacaa      180
gaaaaaaata aagcttttga cttttcaagg ttgcttaaca ggtactgaaa gactggcctc      240
acttaaaactg agccaggaaa agctgcagat ttattaatgg gtgtgttagt gtgcagtgcc      300
t                                                                                   301

```

<210> 255

<211> 302

<212> DNA

<213> Homo sapien

<400> 255

```

agcttttttt tttttttttt tttttttttt ttcattaaaa aatagtgtct tttattataa      60
attactgaaa tgtttctttt ctgaatataa atataaatat gtgcaaagtt tgacttggat      120
tgggattttg ttgagttctt caagcatctc ctaataccct caagggcctg agtagggggg      180
aggaaaaagg actggagggtg gaatctttat aaaaaacaag agtgattgag gcagattgta      240
aacattatta aaaaacaaga aacaaacaaa aaaatagaga aaaaaaccac cccaacacac      300
aa                                                                    302

```

<210> 256

<211> 301

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(301)

<223> n = A,T,C or G

<400> 256

```

gttccagaaa acattgaagg tggcttccca aagtctaact agggataccc cctctagcct      60
aggaccctcc tccccacacc tcaatccacc aaaccatcca taatgcaccc agataggccc      120
acccccaaaa gcctggacac cttgagcaca cagttatgac caggacagac tcctctctat      180
aggcaaatac ctgctggcaa actggcatta cctggtttgt ggggatgggg gggcaagtgt      240
gtggcctctc ggctgggtta gcaagaacat tcagggtagg cctaagttan tcgtgttagt      300
t                                                                    301

```

<210> 257

<211> 301

<212> DNA

<213> Homo sapien

<400> 257

```

gttgtggagg aactctggct tgctcattaa gtcctactga ttttcactat cccctgaatt      60
tccccactta tttttgtctt tcaatatcgc aggccttaga agaggtctac ctgcctccag      120
tcttacctag tccagtctac cccctggagt tagaatggcc atcctgaagt gaaaagtaat      180
gtcacattac tcccttcagt gatctcttgt agaagtgcc atccctgaat gccaccaaga      240
tcttaatctt cacatcttta atcttatctc tttgactcct ctttacaccg gagaaggctc      300
c                                                                    301

```

<210> 258

<211> 301

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(301)

<223> n = A,T,C or G

<400> 258

<210> 262
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 262
 gaggagagcc tgttacagca tttgtaagca cagaatactc caggagtatt tgtaattgtc 60
 tgtgagcttc ttgccgcaag tctctcagaa atttaaaaag atgcaaatac ctgagtcacc 120
 cctagacttc ctaaaccaga tcctctgggg ctggaacctg gcaactctgca tttgtaatga 180
 gggctttctg gtgcacacct aattttgtgc atctttgccc taaatcctgg attagtgtcc 240
 catcattacc cccacattat aatgggatag attcagagca gatactctcc agcaaagaat 300
 c 301

<210> 263
 <211> 301
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(301)
 <223> n = A,T,C or G

<400> 263
 tttagcttgt ggtaaatgac tcacaaaact gattttaaaa tcaagttaat gtgaattttg 60
 aaaattacta cttaatccta attcacaata acaatggcat taagggttga cttgagttgg 120
 ttcttagtat tatttatggg aaataggctc ttaccacttg caaataactg gccacatcat 180
 taatgactga cttcccagta aggctctcta aggggtaagt angaggatcc acaggatttg 240
 agatgctaag gccccagaga tcgtttgatc caaccctctt attttcagag gggaaaatgg 300
 g 301

<210> 264
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 264
 aaagacgtta aaccactcta ctaccacttg tggaactctc aaagggtaaa tgacaaascc 60
 aatgaatgac tctaaaaaca atattttacat ttaatggttt gtagacaata aaaaaacaag 120
 gtggatagat ctagaattgt aacattttta gaaaaccata scatttgaca gatgagaaag 180
 ctcaattata gatgcaaagt tataactaaa ctactatagt agtaaagaaa tacatttcac 240
 acccttcata taaattcact atcttggtct gaggcactcc ataaaatgta tcacgtgcat 300
 a 301

<210> 265
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 265
 tgcccaagtt atgtgtaagt gtatccgcac ccagaggtaa aactacactg tcattcttgt 60


```

<210> 270
<211> 301
<212> DNA
<213> Homo sapien

<400> 270
cattgaagag cttttgcgaa acatcagaac acaagtgcctt ataaaattaa ttaagcctta      60
cacaagaata catattcctt ttattttctaa ggagttaaac atagatgtag ctgatgtgga      120
gagcttgctg gtgcagtgc a tattggataa cactattcat ggccgaattg atcaagtcaa      180
ccaactcctt gaactggatc atcagaagaa ggggtggtgca cgatatactg cactagataa      240
tggaccaacc aactaaattc tctcaccagg ctgtatcagt aaactggcctt aacagaaaac      300
a                                                    301

```

<400> 270

```
<210> 271
<211> 301
<212> DNA
<213> Homo sapien
```

<400> 271

```
<210> 272
<211> 301
<212> DNA
<213> Homo sapien
```

<400> 272

ttaaattgcta	agccacagat	aacaccaatc	aaatggaaca	aatcactgtc	ttcaaattgtc	60
ttatcagaaa	accaaattgag	cctggaatct	tcataatacc	taaacatgcc	gtatttagga	120
tccaataatt	ccctcatgat	gagcaagaaa	aattctttgc	gcacccctcc	tgcatccaca	180
gcatctttct	caacaaatat	aaccttgagt	ggcttcttgt	aatctatgtt	ctttgttttc	240
ctaaggactt	ccattgcac	tcctacaata	ttttctctac	gcaccactag	aattaagcag	300
g						301

```
<220>  
<221> misc_feature  
<222> (1)...(301)  
<223> n = A,T,C or G
```

```
<210> 274
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G
```

```
<210> 275
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G
```

<400>	275						
tcggtgtcag	cagcacgtgg	cattgaacat	tgcaatgtgg	agcccaaacc	acagaaaatg		60
gggtgaaaatt	ggccaacttt	ctattaactt	atgttggcaa	ttttgccacc	aacagtaagc		120
tggcccttct	aataaaagaa	aattgaaagg	tttctcacta	aacggaatta	agtagtggag		180
tcaagagact	cccaggcctc	agcgtacctg	ccggggcggc	cgctcgaagc	cgaattctgc		240

```
<210> 276
<211> 301
<212> DNA
<213> Homo sapien
```

```
<210> 277
<211> 301
<212> DNA
<213> Homo sapien
```

```
<210> 278
<211> 301
<212> DNA
<213> Homo sapien
```

<400>	278						
taccactaca	ctccagcctg	ggcaacagag	caagacctgt	ctcaaagcat	aaaatggaat		60
aacatatcaa	atgaaacagg	gaaaatgaag	ctgacaat	atggaagcca	gggcttgtca		120
cagtctctac	tgttattatg	cattacctgg	gaatttatat	aagcccttaa	taataatgcc		180
aatgaacatc	tcatgtgtgc	tcacaatg	ctggcactat	tataagtgtc	tcacaggttt		240
tatgtgttct	tcgtaacttt	atggantagg	tactcggccg	cgaacacgct	aagccgaatt		300
c							301


```

caggtactac agaattaaaa tactgacaag caagtagttt cttggcgtgc acgaattgca      60
tccagaaccc aaaaattaag aaattcaaaa agacattttg tgggcacctg ctagcacaga      120
agcgcagaag caaagcccag gcagaaccat gctaacctta cagctcagcc tgcacagaag      180
cgcagaagca aagcccaggc agaaccatgc taaccttaca gctcagcctg cacagaagcg      240
cagaagcaaa gcccaggcag aacatgctaa ccttacagct cagcctgcac agaagcacag      300
a                                                                 301

```

```

<210> 283
<211> 301
<212> DNA
<213> Homo sapien

```

```

<400> 283
atctgtatac ggcagacaaa ctttatarag tgtagagagg tgagcgaaag gatgcaaaag      60
cactttgagg gctttataat aatatgctgc ttgaaaaaaa aaatgtgtag ttgatactca      120
gtgcatctcc agacatagta aggggttgct ctgaccaatc aggtgatcat tttttctatc      180
acttcccagg ttttatgcaa aaattttggt aaattctata atgggtgatat gcattcttta      240
ggaaacatat acatttttaa aaatctatct tatgtaagaa ctgacagacg aatttgcttt      300
g                                                                 301

```

```

<210> 284
<211> 301
<212> DNA
<213> Homo sapien

```

```

<400> 284
caggtacaaa acgctattaa gtggccttaga atttgaacat ttgtgggtctt tatttacttt      60
gcttcgtgtg tgggcaaagc aacatcttcc ctaaataatat attaccaaga aaagcaagaa      120
gcagattagg tttttgacaa aacaaacagg ccaaaagggg gctgacctgg agcagagcat      180
ggtgagaggc aaggcatgag agggcaagtt tgttggtggac agatctgtgc ctactttatt      240
actggagtaa aagaaaacaa agttcattga tgtcgaagga tatatacagt gttagaaatt      300
a                                                                 301

```

```

<210> 285
<211> 301
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

```

```

<400> 285
acatcaccat gatcggatcc cccacccatt atacgttgta tgtttacata aatactcttc      60
aatgatcatt agtggtttta aaaaaatact gaaaactcct tctgcatccc aatctctaac      120
caggaagca aatgctatct acagacctgc aagccctccc tcaaacnaaa ctatttctgg      180
attaaatatg tctgacttct tttgagggtc cacgactagg caaatgctat ttacgatctg      240
caaaagctgt ttgaagagtc aaagccccc a tgtgaacacg atttctggac cctgtaacag      300
t                                                                 301

```

<400> 286

```
<210> 287
<211> 301
<212> DNA
<213> Homo sapien
```

<400> 287

```
<210> 288
<211> 301
<212> DNA
<213> Homo sapien
```

<400> 288

```
<210> 289
<211> 301
<212> DNA
<213> Homo sapien
```

<220>

```
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G
```

<400> 289

ggtacactgt ttccatgtta tgtttctaca cattgctacc tcagtgtccc tggaaactta 60

```
<210> 290
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G
```

```
<210> 291
<211> 301
<212> DNA
<213> Homo sapien
```

```
<210> 292
<211> 301
<212> DNA
<213> Homo sapien
```

```

<220>
<221> misc_feature
<222> (1) ... (301)
<223> n = A,T,C or G

<400> 292
accttttagt agtaatgtct aataataaat aagaaatcaa ttttataagg tccatatagc      60
tgtattaaat aattttttaag tttaaaagat aaaataccat catttttaaat gttgggtattc    120
aaaaccaaag natataaccg aaaggaaaaa cagatgagac ataaaatgat ttgcnagatg      180

```



```

ggaaatatag tasttyatga atgttnatta aattccagtt ataatagtgg ctacacactc 240
tcactacaca cacagacccc acagtcctat atgccacaaa cacatttcca taacttgaaa 300
a 301

```

```

<210> 293
<211> 301
<212> DNA
<213> Homo sapien

```

```

<400> 293
ggtaccaagt gctggtgcca gcctgttacc tgttctcact gaaaagtctg gctaattgctc 60
ttgtgtagtc acttctgatt ctgacaatca atcaatcaat ggcttagagc actgactggt 120
aacacaaacg tcactagcaa agtagcaaca gctttaagtc taaatacaaa gctgttctgt 180
gtgagaattt tttaaaaggc tacttgtata ataacccttg tcattttttaa tgtacctcgg 240
ccgcgaccac gctaagccga attctgcaga tatccatcac actggcgggc gctcgagcat 300
g 301

```

```

<210> 294
<211> 301
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

```

```

<400> 294
tgacccataa caatatacac tagctatctt tttaaactgtc catcattagc accaatgaag 60
attcaataaa attaccttta ttcacacatc tcaaaacaat tctgcaaatt cttagtgaag 120
tttaactata gtcacaganc ttaaataatc acattgtttt ctatgtctac tgaaaataag 180
ttcactactt ttctgggata ttctttacaa aatcttatta aaattcctgg tattatcacc 240
ccaattata cagtagcaca accacottat gtagttttta catgatagct ctgtagaggt 300
t 301

```

```

<210> 295
<211> 305
<212> DNA
<213> Homo sapien

```

```

<400> 295
gtactctttc tctcccctcc tctgaattta attctttcaa cttgcaattt gcaaggatta 60
cacatttcac tgtgatgtat attgtgttgc aaaaaaaaaa gtgtctttgt ttaaaattac 120
ttggtttgtg aatccatctt gctttttccc cattggaact agtcattaac ccactctctga 180
actggtagaa aaacrtctga agagctagtc tatcagcatc tgacaggtga attggatggt 240
tctcagaacc atttcaccca gacagcctgt ttctatcctg ttttaataaat tagtttgggt 300
tctct 305

```

```

<210> 296
<211> 301
<212> DNA

```

<213> Homo sapien

<400> 296

```

aggtactatg ggaagctgct aaaataatat ttgatagtaa aagtatgtaa tgtgctatct      60
cacctagtag taaactaaaa ataaactgaa actttatgga atctgaagtt attttccttg      120
attaaataga attaataaac caatatgagg aaacatgaaa ccatgcaatc tactatcaac      180
tttgaaaaag tgattgaacg aaccacttag ctttcagatg atgaacactg ataagtcatt      240
tgtcattact ataaatttta aaatctgtta ataagatggc ctatagggag gaaaaagggg      300
c

```

<210> 297

<211> 300

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(300)

<223> n = A,T,C or G

<400> 297

```

actgagtttt aactggacgc caagcaggca aggctggaag gttttgctct ctttgtgcta      60
aagggttttg aaaccttgaa ggagaatcat tttgacaaga agtacttaag agtctagaga      120
acaaagangt gaaccagctg aaagctctcg ggggaanctt acatgtgttg ttaggcctgt      180
tccatcattg ggagtgcact ggccatccct caaaatttgt ctgggctggc ctgagtgggc      240
accgcacctc ggccgcgacc acgctaagcc gaattctgca gatatccatc acactggcgg      300

```

<210> 298

<211> 301

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(301)

<223> n = A,T,C or G

<400> 298

```

tatggggttt gtcacccaaa agctgatgct gagaaaggcc tccttggggc cctccccgcg      60
ggcatctgag agacctggtg ttccagtgtt tctggaaatg ggtcccagtg ccgccggctg      120
tgaagctctc agatcaatca cgggaagggc ctggcggttg tggccacctg gaaccaccct      180
gtcctgtctg ttacatttc actaycaggt tttctctggg cattacnatt tgttccccta      240
caacagtgac ctgtgcattc tgctgtggcc tgctgtgtct gcaggtggct ctcagcgagg      300
t

```

<210> 299

<211> 301

<212> DNA

<213> Homo sapien

<400> 299

```

gttttgagac ggagtttcac tcttgttgcc cagactggac tgcaatggca ggggtctctgc      60
tactgcacc ctctgcctcc caggttcgag caattctcct gcctcagcct cccaggtagc      120
tgggattgca ggctcacgcc accataccca gctaattttt ttgtattttt agtagagacg      180
gagtttcgcc atgttgggca gctggtctca aactcctgac ctcaagcgac ctgcctgcct      240
cggcctccca aagtgctgga attataggca tgagtcaaca cgcccagcct aaagatattt      300
t                                                                    301

```

<210> 300

<211> 301

<212> DNA

<213> Homo sapien

<400> 300

```

attcagtttt atttgctgcc ccagtatctg taaccaggag tgccacaaaa tcttgccaga      60
tatgtcccac acccactggg aaaggctccc acctggctac ttctctatc agctgggtca      120
gctgcattcc acaaggttct cagcctaatt agtttcaacta cctgccagtc tcaaaactta      180
gtaaagcaag accatgacat tccccacagg aaatcagagt ttgccccacc gtcttgttac      240
tataaagcct gcctctaaca gtccttgctt cttcacacca atcccagcgc catcccccat      300
g                                                                    301

```

<210> 301

<211> 301

<212> DNA

<213> Homo sapien

<400> 301

```

ttaaattttt gagaggataa aaaggacaaa taatctagaa atgtgtcttc ttcagtctgc      60
agaggacccc aggtctccaa gcaaccacat ggtcaagggc atgaataatt aaaagttggg      120
gggaactcac aaagaccctc agagctgaga ccccacaac agtgggagct caciaagacc      180
ctcagagctg agacaccac aacagtggga gctcacaag accctcagag ctgagacacc      240
cacaacagca cctcgttcag ctgccacatg tgtgaataag gatgcaatgt ccagaagtgt      300
t                                                                    301

```

<210> 302

<211> 301

<212> DNA

<213> Homo sapien

<400> 302

```

aggtacacat ttagcttggt gtaaatagact cacaaaactg attttaaaat caagttaatg      60
tgaattttga aaattactac ttaatcctaa ttcacaataa caatggcatt aaggtttgac      120
ttgagttggt tcttagtatt atttatggta aataggctct taccacttgc aaataactgg      180
ccacatcatt aatgactgac ttcccagtaa ggctctctaa ggggtaagta ggaggatcca      240
caggatttga gatgctaagg cccagagat cgtttgatcc aaccctctta ttttcagagg      300
g                                                                    301

```

<210> 303

<211> 301

<212> DNA

<213> Homo sapien

<400> 303
 aggtaccaac tgtggaaata ggtagaggat cattttttct ttccatatca actaagttgt 60
 atattgtttt ttgacagttt aacacatctt cttctgtcag agattctttc acaatagcac 120
 tggctaattg aactaccgct tgcattgttaa aaatggtggt ttgtgaaatg atcataggcc 180
 agtaacgggt atgtttttct aactgatctt ttgctcgttc caaagggacc tcaagacttc 240
 catcgatttt atatctgggg tctagaaaag gagttaatct gttttccctc ataaattcac 300
 c 301

<210> 304
 <211> 301
 <212> DNA
 <213> Homo sapien

<400> 304
 acatggatgt tattttgcag actgtcaacc tgaatttgta tttgcttgac attgcctaatt 60
 tattagtttc agtttcagct taccacattt ttgtctgcaa catgcaraas agacagtgcc 120
 ctttttagtg tatcatatca ggaatcatct cacattgggt tgtgccatta ctggtgcagt 180
 gactttcagc cacttgggta aggtggagtt ggccatatgt ctccactgca aaattactga 240
 ttttcctttt gtaattaata agtgtgtgtg tgaagattct ttgagatgag gtatatactt 300
 c 301

<210> 305
 <211> 301
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(301)
 <223> n = A,T,C or G

<400> 305
 gangtacagc gtggtcaagg taacaagaag aaaaaaatgt gagtggcatc ctgggatgag 60
 cagggggaca gacctggaca gacacgttgt catttgctgc tgtgggtagg aaaatgggcg 120
 taaaggagga gaaacagata caaatctcc aactcagtat taaggatttc tcatgcctag 180
 aatattggta gaaacaagaa tacattcata tggcaaataa ctaaccatgg tggaacaaaa 240
 ttctgggatt taagttggat accaangaaa ttgtattaaa agagctgttc atggaataag 300
 a 301

<210> 306
 <211> 8
 <212> PRT
 <213> Homo sapien

<400> 306
 Val Leu Gly Trp Val Ala Glu Leu
 1 5

<210> 307
 <211> 637
 <212> DNA

<213> Homo sapien

<400> 307

```
acaggggratg aagggaaagg gagaggatga ggaagccccc ctgggggattt ggtttggtcc      60
ttgtgatcag gtggtctatg gggcttatcc ctacaaagaa gaatccagaa atagggggcac      120
attgaggaat gatacttgag cccaaagagc attcaatcat tgttttattt gccttmtttt      180
cacaccattg gtgagggagg gattaccacc ctgggggttat gaagatgggtt gaacacccca      240
cacatagcac cggagatatg agatcaacag tttcttagcc atagagattc acagcccaga      300
gcaggaggac gcttgcacac catgcaggat gacatggggg atgcgctcgg gattggtgtg      360
aagaagcaag gactgttaga ggcaggcttt atagtaacaa gacgggtgggg caaactctga      420
tttccgtggg ggaatgtcat ggtcttgctt tactaagttt tgagactggc aggtagtga      480
actcattagg ctgagaacct tgtggaatgc acttgacca sctgatagag gaagtagcca      540
ggtagggagc tttccagtg ggtgtgggac atatctggca agattttgtg gcactcctgg      600
ttacagatac tggggcagca aataaaaactg aatcttg      637
```

<210> 308

<211> 647

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(647)

<223> n = A,T,C or G

<400> 308

```
acgattttca ttatcatgta aatcggttca ctcaaggggc caaccacagc tgggagccac      60
tgctcagggg aaggttcata tgggactttc tactgoccaa ggttctatac aggatataaa      120
ggngcctcac agtatagatc tggtagcaaa gaagaagaaa caaacactga tctctttctg      180
ccaccctctt gacccttttg aactcctctg acccttttaga acaagcctac ctaatatctg      240
ctagagaaaa gaccaacaac ggccctcaaag gatctcttac catgaaggtc tcagctaatt      300
cttggctaag atgtgggttc cacattaggt tctgaatatg gggggaaggg tcaatttgct      360
cattttgtgt gtggataaag tcaggatgcc cagggggccag agcagggggc tgcttgcttt      420
gggaacaatg gctgagcata taaccatagg ttatggggaa caaaacaaca tcaaagtcac      480
tgtatcaatt gccatgaaga cttgagggac ctgaatctac cgattcatct taaggcagca      540
ggaccagttt gagtggcaac aatgcagcag cagaatcaat ggaaacaaca gaatgattgc      600
aatgtccttt tttttctcct gcttctgact tgataaaagg ggaccgt      647
```

<210> 309

<211> 460

<212> DNA

<213> Homo sapien

<400> 309

```
actttatagt ttaggctgga cattggaaaa aaaaaaaagc cagaacaaca tgtgatagat      60
aatatgattg gctgcacact tccagactga tgaatgatga acgtgatgga ctattgtatg      120
gagcacatct tcagcaagag ggggaaatac tcatcatttt tggccagcag ttgtttgatc      180
accaaacatc atgccagaat actcagcaaa ccttcttagc tcttgagaag tcaaagtcag      240
ggggaattta ttcttgcaa ttttaatttg actccttatg tgagagcagc ggctaccag      300
ctggggtggt ggagcgaacc cgtcactagt ggacatgcag tggcagagct cctggtaacc      360
acctagagga atacacaggc acatgtgtga tgccaagcgt gacacctgta gcactcaaat      420
```

ttgtcttgtt tttgtctttc ggtgtgtaag attcttaagt

460

<210> 310

<211> 539

<212> DNA

<213> Homo sapien

<400> 310

acgggactta	tcaataaaag	ataggaaaag	aagaaaactc	aatattata	ggcagaaatg	60
ctaaaggttt	taaaatatgt	caggattgga	agaaggcatg	gataaagaac	aaagttcagt	120
taggaaagag	aaacacagaa	ggaagagaca	caataaaagt	cattatgtat	tctgtgagaa	180
gtcagacagt	aagattttgt	ggaaatgggt	tggtttgttg	tatggtatgt	attttagcaa	240
taatctttat	ggcagagaaa	gctaaaatcc	tttagcttgc	gtgaatgatc	acttgctgaa	300
ttcctcaagg	taggcatgat	gaaggagggt	ttagaggaga	cacagacaca	atgaactgac	360
ctagatagaa	agccttagta	tactcagcta	ggaatagtga	ttctgagggc	acactgtgac	420
atgattatgt	cattacatgt	atggtagtga	tggggatgat	aggaaggaag	aacttatggc	480
atattttcac	ccccacaaaa	gtcagttaaa	tattgggaca	ctaaccatcc	aggtcaaga	539

<210> 311

<211> 526

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(526)

<223> n = A,T,C or G

<400> 311

caaatttgag	ccaatgacat	agaattttac	aatcaagaa	gcttattctg	gggccatttc	60
ttttgacgtt	ttctctaaac	tactaaagag	gcattaatga	tccataaatt	atattatcta	120
catttacagc	atttaaaatg	tgttcagcat	gaaatattag	ctacagggga	agctaaataa	180
attaaacatg	gaataaagat	ttgtccttaa	atataatcta	caagaagact	ttgatatttg	240
tttttcacaa	gtgaagcatt	cttataaagt	gtcataacct	ttttggggaa	actatgggaa	300
aaaatgggga	aactctgaag	ggttttaagt	atcttacctg	aagctacaga	ctccataacc	360
tctctttaca	gggagctcct	gcagccccta	cagaaatgag	tggctgagat	tcttgattgc	420
acagcaagag	cttctcatct	aaaccctttc	cctttttagt	atctgtgtat	caagtataaa	480
agttctataa	actgtagtnt	acttatttta	atccccaaag	cacagt		526

<210> 312

<211> 500

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(500)

<223> n = A,T,C or G

<400> 312

cctctctctc	cccaccccct	gactctagag	aactggggtt	tctcccagta	ctccagcaat	60
------------	------------	------------	------------	------------	------------	----

```

tcatttctga aagcagttga gccactttat tccaaagtag actgcagatg ttcaaactct 120
ccatttctct ttcccttcca cctgccagtt ttgotgactc tcaacttgct atgagtgtaa 180
gcattaagga cattatgctt cttcgattct gaagacaggc cctgctcatg gatgactctg 240
gcttcttagg aaaatatttt tcttccaaaa tcagtaggaa atctaaactt atccccctct 300
tgcagatgtc tagcagcttc agacatttgg ttaagaacct atgggaaaaa aaaaaatcct 360
tgctaagtgt gtttcctttg taaaccanga ttcttatttg nctggtatag aatatcagct 420
ctgaacgtgt ggtaaagatt tttgtgtttg aatataggag aaatcagttt gctgaaaagt 480
tagtcttaat tatctattgg
500

```

```

<210> 313
<211> 718
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(718)
<223> n = A,T,C or G

```

```

<400> 313
ggagatttgt gtggtttgca gccgagggag accaggaaga tctgcatggt gggaaggacc 60
tgatgataca gaggtgagaa ataagaaagg ctgctgactt taccatctga ggccacacat 120
ctgctgaaat ggagataatt aacatcacta gaaacagcaa gatgacaata taatgtctaa 180
gtagtgacat gtttttgcac atttccagcc cttttaaata tccacacaca caggaagcac 240
aaaaggaagc acagagatcc ctggggagaaa tgcctggccg ccatcttggg tcatcgatga 300
gcctcgccct gtgcctgntc ccgcttgtga gggaaggaca ttagaaaatg aattgatgtg 360
ttccttaaag gatggcagga aaacagatcc tgttgtggat atttatttga acgggattac 420
agatttgaaa tgaagtcaca aagtgcagat taccatgag aggaaaacag acgagaaaat 480
cttgatgggt cacaagacat gcaacaaaca aaatggaata ctgtgatgac acgagcagcc 540
aactggggag gagataccac ggggcagagg tcaggattct ggccctgctg cctaactgtg 600
cgttatacca atcatttcta tttctaccct caaacaagct gtngaataat tgacttacgg 660
ttcttntggc ccacattttc atnatccacc ccttcttttt aannttantc caaantgt 718

```

```

<210> 314
<211> 358
<212> DNA
<213> Homo sapien

```

```

<400> 314
gtttatttac attacagaaa aaacatcaag acaatgtata ctatttcaaa tatatccata 60
cataatcaaa tatagctgta gtacatgttt tcattgggtg agattaccac aaatgcaagg 120
caacatgtgt agatctcttg tcttattctt ttgtctataa tactgtattg tgtagtccaa 180
gctctcggtg gtccagccac tgtgaaacat gctcccttta gattaacctc gtggacgctc 240
ttgttgattt gctgaactgt agtgccctgt attttgcttc tgtctgtgaa ttctgttgct 300
tctggggcat ttccttgtga tgcagaggac caccacacag atgacagcaa tctgaatt 358

```

```

<210> 315
<211> 341
<212> DNA
<213> Homo sapien

```

<400> 315
taccacctcc ccgctggcac tgatgagcgc catcaccatg gtcaccagca ccatgaaggc 60
ataggtgatg atgaggacat ggaatgggcc cccaaggatg gtctgtccaa agaagcgagt 120
gacccccatt ctgaagatgt ctggaacctc taccagcagg atgatgatag ccccaatgac 180
agtcaccagc tccccgacca gccggatatc gtcccttaggg gtcattgtagg cttcctgaag 240
tagcttctgc tgtaagaggg tggtgtcccg ggggctcgtg cggttattgg tcttgggctt 300
gagggggcgg tagatgcagc acatggtgaa gcagatgatg t 341

<210> 316
<211> 151
<212> DNA
<213> Homo sapien

<400> 316
agactgggca agactcttac gcccacact gcaatttggt cttgttgccg tatccattta 60
tgtgggcctt tctcgagttt ctgattataa acaccactgg agcgatgtgt tgactggact 120
cattcaggga gctctggttg caatattagt t 151

<210> 317
<211> 151
<212> DNA
<213> Homo sapien

<400> 317
agaactagtg gatcctaataa aaataacctga aacatatatt ggcatttatc aatggctcaa 60
atcttcattt atctctggcc ttaaccctgg ctctgaggc tgcggccagc agatcccagg 120
ccagggtctt gttcttgcca cacctgcttg a 151

<210> 318
<211> 151
<212> DNA
<213> Homo sapien

<400> 318
actggtggga ggcgctgttt agttggctgt tttcagaggg gtctttcgga gggacctcct 60
gctgcaggct ggagtgtctt tattcctggc gggagaccgc acattccact gctgaggctg 120
tgggggcggt ttatcaggca gtgataaaca t 151

<210> 319
<211> 151
<212> DNA
<213> Homo sapien

<400> 319
aactagtgga tccagagcta taggtacagt gtgatctcag ctttgcaaac acattttcta 60
catagatagt actaggtatt aatagatatg taaagaaaga aatcacacca ttaataatgg 120
taagattggg tttatgtgat tttagtgggt a 151

<210> 320
<211> 150
<212> DNA

<213> Homo sapien

<400> 320

```
aactagtgga tccactagtc cagtgtggtg gaattccatt gtgttggggg tctagatcgc      60
gagcgggctgc cttttttttt tttttttttg ggggggaatt tttttttttt aatagttatt    120
gagtgttcta cagcttacag taaataccat                                     150
```

<210> 321

<211> 151

<212> DNA

<213> Homo sapien

<400> 321

```
agcaactttg tttttcatcc aggttatttt aggcttagga tttcctctca cactgcagtt      60
taggggtggca ttgtaaccag ctatggcata ggtgttaacc aaaggctgag taaacatggg    120
tgcctctgag aaatcaaagt cttcatacac t                                     151
```

<210> 322

<211> 151

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(151)

<223> n = A,T,C or G

<400> 322

```
atccagcatc ttctcctggt tcttgccctc ctttttcttc ttcttasatt ctgcttgagg      60
tttgggcttg gtcagtttgc cacagggctt ggagatggtg acagtcttct ggcattcggc    120
attgtgcagg gctcgcttca nacttccagt t                                     151
```

<210> 323

<211> 151

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(151)

<223> n = A,T,C or G

<400> 323

```
tgaggacttg tkttcctttt ctttatTTTT aatcctctta ckttgtaa atattgccta      60
nagactcant tactaccag tttgtggtt twtgggagaa atgtaactgg acagttagct    120
gttcaatyaa aaagacactt ancccatgtg g                                     151
```

<210> 324

<211> 461

<212> DNA

<213> Homo sapien

004690-004690


```

ggagtccaga cccccagcc cctcctccct cagaccaggg ggtccaggcc cccaaccct      960
cctccctcag actcagaggt ccaagcccc aaccctcct tcccagacc cagaggtcca      1020
ggtcccagcc cctcctccct cagaccagc ggtccaatgc cacctagact ctccctgtac      1080
acagtgcccc cttgtggcac gttgacccaa ccttaccagt tggtttttca ttttttgtcc      1140
ctttcccta gatccagaaa taaagtctaa gagaagcgca aaaaaaaaa aaaaaaaaaa      1200
aaaaaaaaa aaaaaa                                     1215

```

```

<210> 327
<211> 220
<212> PRT
<213> Homo sapien

```

```

<400> 327
Glu Asp Cys Ser Pro His Ser Gln Pro Trp Gln Ala Ala Leu Val Met
 1          5          10          15
Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp Val
 20          25          30
Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly
 35          40          45
Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu
 50          55          60
Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu Leu Ala
 65          70          75          80
Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser Asp
 85          90          95
Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn
100          105          110
Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met Pro
115          120          125
Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu Val Cys
130          135          140
Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala Gly
145          150          155          160
Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly Pro
165          170          175
Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys Ala
180          185          190
Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu Cys Lys
195          200          205
Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
210          215          220

```

```

<210> 328
<211> 234
<212> DNA
<213> Homo sapien

```

```

<400> 328
cgctcgtctc tggtagctgc agccaaatca taaacggcga ggactgcagc ccgcactcgc      60
agccctggca ggcggcactg gtcattgaaa acgaattgtt ctgctcgggc gtcctggtgc      120
atccgcagtg ggtgctgtca gccacacact gtttcagaa ctcctacacc atcgggctgg      180

```



```

gcttcttagc tgaggaaaag cacctccacg ttttgatcaa caatgcagga gtgatgatgt 420
gtccgtactc gaagacagca gatggctttg agatgcacat aggagtcaac cacttgggtc 480
acttcctcct aacccatctg ctgctagaga aactaaagga atcagcccca tcaaggatag 540
taaattgtgtc ttccctcgca catcacctgg gaaggatcca cttccataac ctgcagggcg 600
agaaattcta caatgcaggc ctggcctact gtcacagcaa gctagccaac atcctcttca 660
cccaggaact ggcccggaga ctaaaaggct ctggcggtac gacgtattct gtacaccctg 720
gcacagtcca atctgaactg gttcggcact catctttcat gagatggatg tgggtggcttt 780
tctccttttt catcaagact cctcagcagg gagcccagac cagcctgcac tgtgccttaa 840
cagaaggctct tgagattcta agtgggaatc atttcagtga ctgtcatgtg gcatgggtct 900
ctgcccgaagc tcgtaatgag actatagcaa ggcggtctgt ggacgtcagt tgtgacctgc 960
tgggcctccc aatagactaa caggcagtgc cagttggacc caagagaaga ctgcagcaga 1020
ctacacagta cttcttgtca aaatgattct cttcaagggt tttcaaaacc tttagcacia 1080
agagagcaaa acctccagc cttgcctgct tgggtgtccag ttaaaactca gtgtactgcc 1140
agattcgtct aaatgtctgt catgtccaga tttactttgc ttctgttact gccagagtta 1200
ctagagatat cataatagga taagaagacc ctcatatgac ctgcacagct cattttcctt 1260
ctgaaagaaa ctactaccta ggagaatcta agctatagca gggatgattt atgcaaattt 1320
gaactagctt ctttgttcac aattcagttc ctcccaacca accagtcttc acttcaagag 1380
ggccacactg caacctcagc ttaacatgaa taacaaagac tggctcagga gcagggcttg 1440
cccaggcatg gtggatcacc ggaggtcagt agttcaagac cagcctggcc aacatgggtga 1500
aacccacct ctactaaaaa ttgtgtatat ctttgttgtt cttcctgttt atgtgtgcca 1560
agggagtatt ttcacaaagt tcaaaacagc cacaataatc agagatggag caaaccagt 1620
ccatccagtc tttatgcaaa tgaaatgctg caaagggaag cagattctgt atatgttgg 1680
aactaccac caagagcaca tgggtagcag ggaagaagta aaaaaagaga aggagaatac 1740
tggaagataa tgcacaaaat gaagggacta gttaaggatt aactagccct ttaaggatta 1800
actagttaag gattaatagc aaaagayatt aaatatgcta acatagctat ggaggaattg 1860
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<210> 333

<211> 3030

<212> DNA

<213> Homo sapien

<400> 333

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<210> 334

<211> 2417

<212> DNA

<213> Homo sapien

<400> 334

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<210> 335

<211> 2984

<212> DNA

<213> Homo sapien

<400> 335

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 20 25 30
 Pro Lys Gln Pro Gln Lys Arg Ser Arg Ala Ala Phe Ser His Thr Gln
 35 40 45
 Val Ile Glu Leu Glu Arg Lys Phe Ser His Gln Lys Tyr Leu Ser Ala
 50 55 60
 Pro Glu Arg Ala His Leu Ala Lys Asn Leu Lys Leu Thr Glu Thr Gln
 65 70 75 80
 Val Lys Ile Trp Phe Gln Asn Arg Arg Tyr Lys Thr Lys Arg Lys Gln
 85 90 95
 Leu Ser Ser Glu Leu Gly Asp Leu Glu Lys His Ser Ser Leu Pro Ala
 100 105 110
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 115 120 125
 Ser Tyr Pro Tyr Tyr Pro Tyr Leu Tyr Cys Val Gly Ser Trp Ser Pro
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 Ala Phe Trp
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<210> 337
 <211> 9
 <212> PRT
 <213> Homo sapien

<400> 337
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<210> 338
 <211> 9
 <212> PRT
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<400> 338
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<210> 339
 <211> 318
 <212> PRT
 <213> Homo sapien

<400> 339
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 Cys Thr Ser Thr Val Gln Leu Pro Gly Lys Val Val Val Val Thr Gly
 35 40 45
 Ala Asn Thr Gly Ile Gly Lys Glu Thr Ala Lys Glu Leu Ala Gln Arg
 50 55 60
 Gly Ala Arg Val Tyr Leu Ala Cys Arg Asp Val Glu Lys Gly Glu Leu
 65 70 75 80
 Val Ala Lys Glu Ile Gln Thr Thr Thr Gly Asn Gln Gln Val Leu Val
 85 90 95
 Arg Lys Leu Asp Leu Ser Asp Thr Lys Ser Ile Arg Ala Phe Ala Lys
 100 105 110
 Gly Phe Leu Ala Glu Glu Lys His Leu His Val Leu Ile Asn Asn Ala
 115 120 125
 Gly Val Met Met Cys Pro Tyr Ser Lys Thr Ala Asp Gly Phe Glu Met
 130 135 140
 His Ile Gly Val Asn His Leu Gly His Phe Leu Leu Thr His Leu Leu
 145 150 155 160
 Leu Glu Lys Leu Lys Glu Ser Ala Pro Ser Arg Ile Val Asn Val Ser
 165 170 175
 Ser Leu Ala His His Leu Gly Arg Ile His Phe His Asn Leu Gln Gly
 180 185 190
 Glu Lys Phe Tyr Asn Ala Gly Leu Ala Tyr Cys His Ser Lys Leu Ala
 195 200 205
 Asn Ile Leu Phe Thr Gln Glu Leu Ala Arg Arg Leu Lys Gly Ser Gly
 210 215 220
 Val Thr Thr Tyr Ser Val His Pro Gly Thr Val Gln Ser Glu Leu Val
 225 230 235 240
 Arg His Ser Ser Phe Met Arg Trp Met Trp Trp Leu Phe Ser Phe Phe
 245 250 255
 Ile Lys Thr Pro Gln Gln Gly Ala Gln Thr Ser Leu His Cys Ala Leu
 260 265 270
 Thr Glu Gly Leu Glu Ile Leu Ser Gly Asn His Phe Ser Asp Cys His
 275 280 285
 Val Ala Trp Val Ser Ala Gln Ala Arg Asn Glu Thr Ile Ala Arg Arg
 290 295 300
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<210> 340

<211> 483

<212> DNA

<213> Homo sapien

<400> 340

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ctcctgctgc aggctggagt gtctttattc ctggcgggag accgcacatt ccaactgctga      180
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ccttcaattt tctctttggc tgacgacgga gtccgtggtg tcccgatgta actgaccct      300
gctccaaacg tgacatcact gatgctcttc tcgggggtgc tgatggccc cttggtcacg      360
tgctcaatct cgccattoga ctcttgctcc aaactgtatg aagacacctg actgcacgtt      420

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ctg 483

<210> 341
<211> 344
<212> DNA
<213> Homo sapien

<400> 341
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gctgccttac aagtattaaa tattttactt ctttccataa agagtagctc aaaatatgca 180
attaatttaa taattttctga tgatgggttt atctgcagta atatgtatat catctattag 240
aatttactta atgaaaaact gaagagaaca aaatttgtaa ccactagcac ttaagtactc 300
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<210> 342
<211> 592
<212> DNA
<213> Homo sapien

<400> 342
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<210> 343
<211> 382
<212> DNA
<213> Homo sapien

<400> 343
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aaaccaccaa gctgaaaaaa aa 382

<210> 344
<211> 536
<212> DNA
<213> Homo sapien

<400> 344

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gtttaggggg atgccaagga taaggccagc tcagttatat gaagagaagc agaacaaaca      180
agtcctttcag agaaatggat gcaatcagag tgggatcccg gtcacatcaa ggtcacactc      240
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caactaacct gccactaata gttatgtcat cctctcttatt aatcatcatc ctagccctaa      480
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<210> 345

<211> 251

<212> DNA

<213> Homo sapien

<400> 345

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gcgtgggcca ggaaatcaca tcctacactg cccaggagcc agacacattt atggaacaga      180
aaataacata tcggttttgg agagacactg ccaactggct ggagattaat ccggacactg      240
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<210> 346

<211> 282

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(282)

<223> n = A,T,C or G

<400> 346

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agggagacta tacctggctc ttgccctaag tgagaggtct tcctcccgcc accaaaaaat      180
agaaaggctt tctatttcac tggcccaggt agggggaagg agagtaactt tgagtctgtg      240
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<210> 347

<211> 201

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(201)

<223> n = A,T,C or G

aatcgag

908

<210> 351

<211> 472

<212> DNA

<213> Homo sapien

<400> 351

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cattaacttg	attttaaaat	cagwtttgyg	agtcatttac	cacaagctaa	atgtgtacac		180
tatgataaaa	acaaccattg	tattcctgtt	tttctaaaca	gtcctaattt	ctaactctgt		240
atatatcctt	cgacatcaat	gaactttgtt	ttcttttact	ccagtaataa	agtaggcaca		300
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tcagccccct	tttggcctgt	ttgttttgtc	aaaaaccta	tctgcttctt	gcttttcttg		420
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<210> 352

<211> 251

<212> DNA

<213> Homo sapien

<400> 352

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aataagcaca	a					251

<210> 353

<211> 436

<212> DNA

<213> Homo sapien

<400> 353

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<210> 354

<211> 854

<212> DNA

<213> Homo sapien

<400> 354

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atatcaactg	cataaatgta	aaatgcatgt	gacccaagaa	ggcccaaaag	tggcagacaa	780
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<210> 355

<211> 676

<212> DNA

<213> Homo sapien

<400> 355

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atccacaagt	catacctgga	tgtcagcgaa	gagggcacgg	aggcagcagc	agccactggg	180
gacagcatcg	ctgtaaaaaag	cctaccaatg	agagctcagt	tcaaggcgaa	ccacccttcc	240
ctgttcttta	taaggcacac	tcataccaac	acgatcctat	tctgtggcaa	gcttgccctct	300
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<210> 356

<211> 574

<212> DNA

<213> Homo sapien

<400> 356

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caagcttccc	atttgtagat	ctcagtgcct	atgagtatct	gacacctgtt	cctctcttca	180
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ttcttctgtc	tctgcctaga	ctggaataaa	aagccaatct	ctctcgtggc	acaggaagg	420
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gatagacggc	acagggagct	cttaggtcag	cgctgctggg	tggaggacat	tcctgagtcc	540
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<210> 357
 <211> 393
 <212> DNA
 <213> Homo sapien

<400> 357
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 atagatataa ttattccagt ttttttaaaa cttaaaarat attccattgc cgaattaara 240
 araarataag tgttatatgg aaagaagggc attcaagcac actaaaraaa cctgaggkaa 300
 gcataatctg tacaaaatta aactgtcctt ttgggcattt taacaaattt gcaacgktct 360
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<210> 358
 <211> 630
 <212> DNA
 <213> Homo sapien

<400> 358
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 tcaactgaagg gagtaatgtg acattacttt tcaacttcagg atggccattc taactccagg 480
 gggtagactg gactaggtaa gactggaggc aggtagacct cttctaaggc ctgcatagtg 540
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 caagccagag gttcctccac aacaaccagt 630

<210> 359
 <211> 620
 <212> DNA
 <213> Homo sapien

<400> 359
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 aatgtaagat aactttataa gaattctggg tcaaataaaa ttctttgaag aaaacatcca 480
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 ctgtaagat gtgacagtgt 620

<210> 360

<211> 431
 <212> DNA
 <213> Homo sapien

<400> 360
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 tactcatcat ttttggccag cagttgtttg atcaccaaac atcatgccag aatactcagc 180
 aaaccttctt agctcttgag aagtcaaagt cggggggaat ttattcctgg caattttaat 240
 tggactcctt atgtgagagc agcggctacc cagctggggt ggtggagcga acccgctcact 300
 agtggacatg cagtggcaga gtcctgggta accacctaga ggaatacaca ggcacatgtg 360
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<210> 361
 <211> 351
 <212> DNA
 <213> Homo sapien

<400> 361
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 ttgacttcct ccggggcttt ccgaggggct tcaccgtgag ccctgcggcc ctcagggctg 240
 caatcctgga ttcaatgtct gaaacctcgc tctctgcctg ctggacttct gagggcgtca 300
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<210> 362
 <211> 463
 <212> DNA
 <213> Homo sapien

<400> 362
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 ccccggtcac agaaatgacc aggttgggtg ttttcagggt ccagtgtctg gtcagcagct 180
 cgtaaaggat ttccgcgtcc gtgtcgcagg acagacgtat atacttcctt ttcttcccca 240
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<210> 363
 <211> 653
 <212> DNA
 <213> Homo sapien

<220>
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<213> Homo sapien

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acgtgcatag	taaatcttta	tatttgctat	ggcgttgcac	tagaggactt	ggactgcaac	360
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<213> Homo sapien

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<213> Homo sapien

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<210> 367

<211> 668

<212> DNA

<213> Homo sapien

<400> 367

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accrtataag agcagtgtt tggccattaa tttatcttcc attrtagaca gcrtagtgya     180
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gcagtcctat gagagtgaga agacttttta ggaaattgta gtgcactagc tacagccata     600
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<210> 368

<211> 1512

<212> DNA

<213> Homo sapien

<400> 368

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<210> 369

<211> 1853

<212> DNA

<213> Homo sapien

<400> 369

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<210> 370

<211> 2184

<212> DNA

<213> Homo sapien

<400> 370

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<210> 371

<211> 1855

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(1855)

<223> n = A,T,C or G

<400> 371

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<210> 372
 <211> 1059
 <212> DNA
 <213> Homo sapien

<400> 372

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<210> 373
 <211> 1155
 <212> DNA
 <213> Homo sapien

<400> 373

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1155

<210> 374

<211> 2000

<212> DNA

<213> Homo sapien

<400> 374

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<210> 375

<211> 2040

<212> DNA

<213> Homo sapien

<400> 375

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<210> 376

<211> 329

<212> PRT

<213> Homo sapien

<400> 376

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Glu Tyr Thr Ile Val His Ala Ser Phe Ile Ser Cys Ile Ser Ser Ser
      35             40             45
Leu Asp Gly Gln Gly Glu Arg Gln Glu Gln Arg Gly His Phe Trp Arg
      50             55             60
Pro Gln Arg Leu Leu Cys Glu Asp Ala Trp Glu Gln Glu Val Gln Val
65             70             75             80
Val Leu Pro Leu Leu Pro Leu Leu Gln Gly Ser Gly Lys Ser Asn Val
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Val Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe Met Asp Pro Arg Tyr
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His Val His Gly Glu Asp Leu Asp Lys Leu His Arg Ala Ala Trp Trp
      115                      120                      125
Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met Leu Arg Asp Thr Asp
      130                      135                      140
Val Asn Lys Arg Asp Lys Gln Lys Arg Thr Ala Leu His Leu Ala Ser
      145                      150                      155                      160
Ala Asn Gly Asn Ser Glu Val Val Lys Leu Val Leu Asp Arg Arg Cys
      165                      170                      175
Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr Ala Leu Thr Lys Ala
      180                      185                      190
Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met Leu Leu Glu His Gly
      195                      200                      205
Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr
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Ala Val Tyr Asn Glu Asp Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr
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Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu
      245                      250                      255
Leu Gly Ile His Glu Gln Lys Gln Gln Val Val Lys Phe Leu Ile Lys
      260                      265                      270
Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu
      275                      280                      285
Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile Val Ser Pro Leu Leu
      290                      295                      300
Glu Gln Asn Val Asp Val Ser Ser Gln Asp Leu Glu Arg Arg Pro Glu
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Ser Met Leu Phe Leu Val Ile Ile Met
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<210> 377

<211> 148

<212> PRT

<213> Homo sapien

<220>

<221> VARIANT

<222> (1)...(148)

<223> Xaa = Any Amino Acid

<400> 377

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      20                      25                      30
Asp Leu Ile Val Met Leu Arg Asp Thr Asp Val Asn Lys Xaa Asp Lys
      35                      40                      45
Gln Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu
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Val Val Lys Leu Xaa Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp

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Asn Gly Asp Asn Gly Leu Ile Pro Gln Arg Lys Ser Arg Thr Pro Glu
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 Asn Gln Gln Phe Pro Asp Asn Glu Ser Glu Glu Tyr His Arg Ile Cys
 1505 1510 1515 152
 Glu Leu Val Ser Asp Tyr Lys Glu Lys Gln Met Pro Lys Tyr Ser Ser
 1525 1530 1535
 Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu
 1540 1545 1550
 Ser Gln Arg Leu Glu Gly Ser Glu Asn Gly Gln Pro Glu Lys Arg Ser
 1555 1560 1565
 Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Leu Glu Asn Phe
 1570 1575 1580
 Met Ala Ile Glu Glu Met Lys Lys His Gly Ser Thr His Val Gly Phe
 1585 1590 1595 160
 Pro Glu Asn Leu Thr Asn Gly Ala Thr Ala Gly Asn Gly Asp Asp Gly
 1605 1610 1615
 Leu Ile Pro Pro Arg Lys Ser Arg Thr Pro Glu Ser Gln Gln Phe Pro
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 1635 1640 1645
 Lys Gln Phe Cys Glu Glu Gln Asn Thr Gly Ile Leu His Asp Glu Ile
 1650 1655 1660
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 1665 1670 1675 168
 Glu Leu Ser Leu Ser Cys Lys Lys Glu Lys Asp Ile Leu His Glu Asn
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 Met Lys His Gln Ser Gln Leu
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<210> 379

<211> 656

<212> PRT

<213> Homo sapien

<400> 379

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 Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp
 35 40 45
 His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp
 50 55 60
 Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val
 65 70 75 80
 Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn
 85 90 95
 Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arg Gly Ser
 100 105 110

		515					520					525				
Lys	His	Gly	Ser	Thr	His	Val	Gly	Phe	Pro	Glu	Asn	Leu	Thr	Asn	Gly	
	530					535					540					
Ala	Thr	Ala	Gly	Asn	Gly	Asp	Asp	Gly	Leu	Ile	Pro	Pro	Arg	Lys	Ser	
545					550					555					560	
Arg	Thr	Pro	Glu	Ser	Gln	Gln	Phe	Pro	Asp	Thr	Glu	Asn	Glu	Glu	Tyr	
				565					570					575		
His	Ser	Asp	Glu	Gln	Asn	Asp	Thr	Gln	Lys	Gln	Phe	Cys	Glu	Glu	Gln	
			580					585				590				
Asn	Thr	Gly	Ile	Leu	His	Asp	Glu	Ile	Leu	Ile	His	Glu	Glu	Lys	Gln	
		595					600					605				
Ile	Glu	Val	Val	Glu	Lys	Met	Asn	Ser	Glu	Leu	Ser	Leu	Ser	Cys	Lys	
	610					615					620					
Lys	Glu	Lys	Asp	Ile	Leu	His	Glu	Asn	Ser	Thr	Leu	Arg	Glu	Glu	Ile	
625					630					635					640	
Ala	Met	Leu	Arg	Leu	Glu	Leu	Asp	Thr	Met	Lys	His	Gln	Ser	Gln	Leu	
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<210> 380
<211> 671
<212> PRT
<213> Homo sapien
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1				5					10					15				
Pro	Phe	Gly	Leu	Arg	Ser	Lys	Met	Gly	Lys	Trp	Cys	Cys	Arg	Cys	Phe			
			20					25					30					
Pro	Cys	Cys	Arg	Glu	Ser	Gly	Lys	Ser	Asn	Val	Gly	Thr	Ser	Gly	Asp			
		35				40						45						
His	Asp	Asp	Ser	Ala	Met	Lys	Thr	Leu	Arg	Ser	Lys	Met	Gly	Lys	Trp			
	50					55					60							
Cys	Arg	His	Cys	Phe	Pro	Cys	Cys	Arg	Gly	Ser	Gly	Lys	Ser	Asn	Val			
65					70					75				80				
Gly	Ala	Ser	Gly	Asp	His	Asp	Asp	Ser	Ala	Met	Lys	Thr	Leu	Arg	Asn			
				85					90					95				
Lys	Met	Gly	Lys	Trp	Cys	Cys	His	Cys	Phe	Pro	Cys	Cys	Arg	Gly	Ser			
			100					105					110					
Gly	Lys	Ser	Lys	Val	Gly	Ala	Trp	Gly	Asp	Tyr	Asp	Asp	Ser	Ala	Phe			
		115					120					125						
Met	Glu	Pro	Arg	Tyr	His	Val	Arg	Gly	Glu	Asp	Leu	Asp	Lys	Leu	His			
	130					135					140							
Arg	Ala	Ala	Trp	Trp	Gly	Lys	Val	Pro	Arg	Lys	Asp	Leu	Ile	Val	Met			
145					150					155					160			
Leu	Arg	Asp	Thr	Asp	Val	Asn	Lys	Lys	Asp	Lys	Gln	Lys	Arg	Thr	Ala			
				165					170					175				
Leu	His	Leu	Ala	Ser	Ala	Asn	Gly	Asn	Ser	Glu	Val	Val	Lys	Leu	Leu			
			180					185					190					
Leu	Asp	Arg	Arg	Cys	Gln	Leu	Asn	Val	Leu	Asp	Asn	Lys	Lys	Arg	Thr			
		195					200					205						
Ala	Leu	Ile	Lys	Ala	Val	Gln	Cys	Gln	Glu	Asp	Glu	Cys	Ala	Leu	Met			

Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser Leu Ser Cys Lys Lys
 625 630 635 640
 Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu Arg Glu Glu Ile Ala
 645 650 655
 Met Leu Arg Leu Glu Leu Asp Thr Met Lys His Gln Ser Gln Leu
 660 665 670

<210> 381
 <211> 251
 <212> DNA
 <213> Homo sapien

<400> 381
 ggagaagcgt ctgctggggc aggaaggggt ttccctgccc tctcacctgt cctcaccac 60
 ggtaacatgc ttcccctaag ggtatcccaa cccagggggc tcaccatgac ctctgagggg 120
 ccaatatccc aggagaagca ttggggaggt gggggcaggt gaaggaccca ggactcacac 180
 atcctggggc tccaaggcag aggagaggggt cctcaagaag gtcaggagga aaatccgtaa 240
 caagcagtca g 251

<210> 382
 <211> 3279
 <212> DNA
 <213> Homo sapiens

<400> 382
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 cactgggagg ggacatcctg cagaaggtag gagtgcagca acacccgctg caggggaggg 180
 gagagccctg cggcacctgg gggagcagag ggagcagcac ctgcccaggc ctgggaggag 240
 gggcctggag ggcgtgagga ggagcgaggg ggctgcattg ctggagttag ggatcagggg 300
 cagggcgcgga gatggcctca cacaggggaag agagggcccc tctgcaggg cctcacctgg 360
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 aagaaggaca gggcctggct caggtgtcca gaggtgtcg ctggcttccc tttgggatca 480
 gactgcaggg agggagggcg gcagggttgt ggggggagtg acgatgagga tgacctgggg 540
 gtggctccag gccttgcccc tgcttggggc ctacccagc ctccctcaca gtctcctggc 600
 cctcagtctc tccccccac tccatcctcc atctggcctc agtgggtcat tctgatcact 660
 gaactgacca taccagccc tgcccacggc cctccatggc tccccaatgc cctggagagg 720
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acacacagca aggttgacgc tgtaaacata gccacgctg tcctgggggc actgggaagc 1740
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cgtcagattt gatgatttcc tagcaggact tacagaaata aagagctatc atgctgtggt 1920
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<210> 383

<211> 155

<212> PRT

<213> Homo sapiens

<400> 383

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Gly Lys Arg Gly Pro Leu Leu Gln Gly Leu Thr Trp Ala Thr Gly Gly
20 25 30

His Cys Phe Ser Ser Glu Glu Ser Gly Ala Val Asp Gly Ala Gly Gln
35 40 45

Lys Lys Asp Arg Ala Trp Leu Arg Cys Pro Glu Ala Val Ala Gly Phe
50 55 60

Pro Leu Gly Ser Asp Cys Arg Glu Gly Gly Arg Gln Gly Cys Gly Gly
65 70 75 80

Ser Asp Asp Glu Asp Asp Leu Gly Val Ala Pro Gly Leu Ala Pro Ala
 85 90 95

Trp Ala Leu Thr Gln Pro Pro Ser Gln Ser Pro Gly Pro Gln Ser Leu
 100 105 110

Pro Ser Thr Pro Ser Ser Ile Trp Pro Gln Trp Val Ile Leu Ile Thr
 115 120 125

Glu Leu Thr Ile Pro Ser Pro Ala His Gly Pro Pro Trp Leu Pro Asn
 130 135 140

Ala Leu Glu Arg Gly His Leu Val Arg Glu
 145 150

<210> 384

<211> 557

<212> DNA

<213> Homo sapiens

<400> 384

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ggatcctcta gagcgccgc ctactactac taaattcgcg gccgcgtcga cgaagaagag 60
aaagatgtgt tttgttttgg actctctgtg gtcccttcca atgctgtggg tttccaacca 120
ggggaagggt cccttttgca ttgccaagtg ccataaccat gagcactact ctaccatggg 180
tctgcctcct ggccaagcag gctggtttgc aagaatgaaa tgaatgattc tacagctagg 240
acttaacctt gaaatggaaa gtcttgcaat cccatttgca ggatccgtct gtgcacatgc 300
ctctgtagag agcagcattc ccagggacct tggaaacagt tggcactgta aggtgcttgc 360
tccccaagac acatcctaaa aggtgttgta atgggtgaaaa cgtcttccctt ctttattgcc 420
ccttcttatt tatgtgaaca actgtttgtc tttttttgta tcttttttaa actgtaaagt 480
tcaattgtga aaatgaatat catgcaaata aattatgcga ttttttttcc aaagtaaaaa 540
aaaaaaaaaa aaaaaaaa                                     557
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<210> 385

<211> 337

<212> DNA

<213> Homo sapiens

<400> 385

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ttcccagggt atgtgcgagg gaagacacat ttactatcct tgatggggct gattccttta 60
gtttctctag cagcagatgg gttaggagga agtgacccaa gtggttgact cctatgtgca 120
tctcaaagcc atctgctgtc ttcgagtaag gacacatcat cactcctgca ttgttgatca 180
aaacgtggag gtgcttttcc tcagctaaga agcccttagc aaaagctcga atagacttag 240
tatcagacag gtccagtttc cgcaccaaca cctgctgggt ccctgtcgtg gtctggatct 300
ctttggccac caattccccc ttttccacat cccggca                                     337
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<210> 386

<211> 300

<212> DNA

<213> Homo sapiens

gggcccgcta	ccggcccagg	ccccgcctcg	cgagtcctcc	tccccgggtg	cctgcccgca	60
gcccgctcgg	cccagagggg	gggcgcgggg	ctgcctctac	cggctggcgg	ctgtaactca	120
gcgaccttg	cccgaaggct	ctagcaagga	cccaccgacc	ccagccgcgg	cggcggcggc	180
gcggactttg	cccggtgtgt	ggggcggagc	ggactgcgtg	tccgcggacg	ggcagcgaag	240
atgttagcct	tcgctgccag	gaccgtggac	cgatcccagg	gctgtggtgt	aacctcaqcc	300

<213> Homo sapiens

gggcccagtc	gggcaccaag	ggactctttg	caggcttcct	tcctcggatc	atcaaggctg	60
ccccctcctg	tgccatcatg	atcagcacct	atgagttcgg	caaaagcttc	ttccagaggc	120
tgaaccagga	cgggttctg	ggcggctgaa	aggggcaagg	aggcaaggac	cccgtctctc	180
ccacggatgg	ggagagggca	ggaggagacc	cagccaagtg	ccttttcctc	agcactgagg	240
gagggggctt	gtttcccttc	cctcccggcg	acaagctcca	gggcaggggt	gtccctctgg	300
gcggcccagc	acttcctcag	acacaacttc	ttctgctgtc	tccagtctgt	gggatcatca	360
cttaccacc	ccccagttc	aagaccaa	cttcagctg	cccccttctg	gtttccctgt	420
gtttgctgta	gctgggcag	tctccaggaa	ccaagaagcc	ctcagcctgg	tgtagtctcc	480
ctgacccttg	ttaattcctt	aagtctaaag	atgatgaact	tcaaaaaaaaa	aaaaaaaa	537

<213> Homo sapiens

aggataattt	ttaaaccaat	caaataaaaa	aaacaaacaa	acaaaaaagg	aaatgtcatg	60
tgagggttaa	ccagtttgca	ttccccaat	gtggaaaaaag	taagaggact	actcagcact	120
gtttgaagat	tgcctcttct	acagcttctg	agaatttgtgt	tatttcactt	gccaagtga	180
ggacccccct	cccaacatgc	cccagcccac	ccctaagcat	ggccccctgt	caccaggcaa	240
ccaggaaaact	gtactttgtg	gacctacca	gagaccagga	gggtttgggt	agctcacagg	300
acttccccca	cccagaaga	ttagcatccc	atactagact	catactcaac	tcaactaggc	360
tcatactcaa	ttgatggtta	ttagacaatt	ccatttcttt	ctggttatta	taaacagaaa	420
atctttctct	ttctcattac	cagtaaaggc	tcttggtatc	ttctctgttg	aatgatttct	480
atgaacttgt	cttattttta	tgggtgggtt	ttttcttgtt			520

<213> Homo sapiens

cggtgcccc	gtttgacaga	aggaaaggcg	gagcttattc	aaagtctaga	gggagtgagg	60
gagttaaggc	tggatttcag	atctgcctgg	ttccagccgc	agtgtgccct	ctgctccccc	120
aacgactttc	caaataatct	caccagcgcc	ttccagctca	ggcgctctag	aagcgctctt	180
aagcctatgg	ccagctgtct	ttgtgttccc	tctcacccgc	ctgtcctcac	agctgagact	240
cccaggaaac	cttcagacta	ccttctctct	ccttcagcaa	ggggcggttg	ccacattctc	300
tgagggtcag	tggaagaacc	tagactccca	ttgctagagg	tagaaagggg	aagggtgctg	360

gggag

365

<210> 390

<211> 221

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(221)

<223> n = A,T,C or G

<400> 390

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tgcctctcca tcctggcccc gacttctctg tcaggaaagt ggggatggac cccatctgca 60
tacacggntt ctcatgggtg tggaacatct ctgcttgagg ttccaggaag gcctctggct 120
gctctangag tctgancnga ntcgttgccc cantntgaca naaggaaagg cggagcttat 180
tcaaagtcta gagggagtgg aggagttaag gctggatttc a 221

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<210> 391

<211> 325

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(325)

<223> n = A,T,C or G

<400> 391

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tggagcaggt cccgaggcct ccctagagcc tggggccgac tctgtgncga tgcangcttt 60
ctctcgcgcc cagcctggag ctgctcctgg catctaccaa caatcagncg aggcgagcag 120
tagccagggc actgctgcca acagccagtc cnnataccat catgtnaccc ggtgngctct 180
naanttngat ntccanagcc ctacccatcn tagttctgct ctcccaccgg ntaccagccc 240
cactgcccag gaatcctaca gccagtaccc tgtcccgacg tctctaccta ccagtacgat 300
gagacctccg gctactacta tgacc 325

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<210> 392

<211> 277

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(277)

<223> n = A,T,C or G

<400> 392

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agtctcactt nggnagnngn ctctactttg agtctcttcc ccggcctggn ccagtngnaa 120
antaccanga accgncatgn cttaanaacn ncctggtttn tgggttnntc aatgactgca 180
tgacgtgcac caccctgtcc actacgtgat gctgtaggat taaagtctca cagtgggcgg 240

```

277

<213> Homo sapiens

actagttccag	tgtgggtggaa	ttcgcgggccg	cgtcgacgga	caggtcagct	gtctgggtca	60
gtgatctaca	ttctgaagtt	gtctgaaaat	gtcttcatga	ttaaattcag	cctaaacgtt	120
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gaggggtcta	ggagatctgt	ccctttttaga	gacaccttac	ttataatgaa	gtatttgga	300
gggtggtttt	caaaagtaga	aatgtcctgt	attccgatga	tcattcctgta	aacattttat	360
catttattaa	tcattcctgc	ctgtgtctat	tattatattc	atatctctac	gctggaaact	420
ttctgcctca	atgtttactg	tgcctttgtt	tttgctagtt	tgtgttggtg	aaaaaaaaaa	480
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ttttgcctat	caaaaaaaaaa	aaaaaa				566

<213> Homo sapiens

<223> n = A, T, C or G

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gcaggaggac	cgggcttttaa	ggagtttttaa	gctgagtgtc	actgtagacc	ccaaatacca	180
tcccaagatt	atcgggagaa	agggggcagt	aattacccaa	atccggttgg	agcatgacgt	240
gaacatccag	tttctgata	aggacgatgg	gaaccagccc	caggaccaaa	ttaccatcac	300
agggtacgaa	aagaacacag	aagctgccag	ggatgctata	ctgagaattg	tgggtgaact	360
tgagcagatg	gtttctgagg	acgt				384

<213> Homo sapiens

ggcaaaactg	tgtgacctca	ataagacctc	gcagatccaa	ggtcaagtat	cagaagtgac	60
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tatcagaggt	ttcatcattg	cggaaattgt	ggagtctaag	gaaatcatgg	cctctgaagt	180
attcacgtct	ttccagtacc	ctgagttctc	tatagagttg	cctaacacag	gcagaattgg	240
ccagctactt	gtctgcaatt	gtatcttcaa	gaataccctg	gccatccctt	tgactgacgt	300
caagttctct	ttggaaagcc	tgggcatctc	ctcactacag	acctctgacc	atgggacggt	360
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<220>
 <221> misc_feature
 <222> (1)...(183)
 <223> n = A,T,C or G

<400> 408
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 cattatcctt ccagtattcn ccttctnttt tatttactcc ttcttggtta cccatgtact 180
 ntt 183

<210> 409
 <211> 250
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(250)
 <223> n = A,T,C or G

<400> 409
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 gtccctcctt caacaacata ggaggatcct ccccttcttt ctgctcacgg ccttatctag 180
 gcttcccagt gccccagga cagcgtgggc tatgtttaca gcgcntcctt gctggggggg 240
 ggccttatgc 250

<210> 410
 <211> 306
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(306)
 <223> n = A,T,C or G

<400> 410
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 agtcttgcaa tcccatattgc aggatccgtc tgtgcacatg cctctgtaga gagcagcatt 120
 cccagggacc ttggaaacag ttggcactgt aagggtgctt ctcccccaaga cacatcctaa 180
 aagggtgttg aatggtgaaa accgcttcct tctttattgc cccttcttat ttatgtgaac 240
 nactggttgg ctttttttgn atctttttta aactggaaag ttcaattgng aaaatgaata 300
 tcntgc 306

<210> 411
 <211> 261
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(261)
 <223> n = A,T,C or G

<400> 411
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 ggatcttttg tatttaagga ttctgagatt ttgcttgagc aggattagat aaggctgttc 120
 tttaaatgtc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
 aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttaccat cagttccagc 240
 cttctctcaa ggngaggcaa a 261

<210> 412
 <211> 241
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(241)
 <223> n = A,T,C or G

<400> 412
 gttcaatggt acctgacatt tctacaacac cccactcacc gatgtattcg ttgcccagtg 60
 ggaacatacc agcctgaatt tggaaaaaat aattgtgttt cttgcccagg aaatactacg 120
 actgactttg atggctccac aaacataacc cagtgtaaaa acagaagatg tggaggggag 180
 ctgggagatt tctactgggtta cattgaattc ccaaactacc cangcaatta cccagccaac 240
 a 241

<210> 413
 <211> 231
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(231)
 <223> n = A,T,C or G

<400> 413
 aactcttaca atccaagtga ctcatctgtg tgcttgaatc ctttccactg tctcatctcc 60
 ctcatccaag tttctagtag cttctctttg ttgtgaagga taatcaaact gaacaacaaa 120
 aagtttactc tctctatttg gaacctaaaa actctcttct tcctgggtct gagggctcca 180
 agaatccttg aatcanttct cagatcattg gggacaccan atcaggaacc t 231

<210> 414
 <211> 234
 <212> DNA
 <213> Homo sapiens

<400> 414


```

gccaaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attcttgaat gagtcctata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg aagtgcctatg acaaacctgg caagcccg 408

```

<210> 421

<211> 352

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(352)

<223> n = A,T,C or G

<400> 421

```

gctcaaaaat ctttttactg atnggcatgg ctacacaatc attgactatt acggaggcca 60
gaggagaatg aggcctggcc tgggagccct gtgcctacta naagcacatt agattatcca 120
ttcactgaca gaacaggtct tttttgggtc cttcttctcc accacnatac acttgcagtc 180
ctccttcttg aagattcttt ggcagttgtc tttgtcataa cccacaggtg tagaaacaag 240
ggtgcaacat gaaatttctg tttcgtagca agtgcctgtc tcacaagttg gcangtctgc 300
cactccgagt ttattgggtg tttgtttcct ttgagatcca tgcatttctc gg 352

```

<210> 422

<211> 337

<212> DNA

<213> Homo sapiens

<400> 422

```

atgccaccat gctggcaatg cagcggggcgg tcgaaggcct gcatatccag cccaagctgg 60
cgatgatcga cggcaaccgt tgcccgaagt tgccgatgcc agccgaagcg gtggtcaagg 120
gcatagcaa ggtgccggcg atcgcggcgg cgtcaatcct ggccaaggtc agccgtgatc 180
gtgaaatggc agctgtcgaa ttgatctacc cgggttatgg catcggcggg cataagggtc 240
atccgacacc ggtgcacctg gaagccttgc agcggctggg gccgacgccg attcaccgac 300
gcttcttccg ccggtacggc tggcctatga aaattat 337

```

<210> 423

<211> 310

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(310)

<223> n = A,T,C or G

<400> 423

```

gctcaaaaat ctttttactg atatggcatg gctacacaat cattgactat tagaggccag 60
aggagaatga ggcctggcct gggagccctg tgccctactan aagcncatta gattatccat 120
tcactgacag aacaggtctt ttttgggtcc ttcttctcca ccacgatata cttgcagtc 180
tccttcttga agattctttg gcagttgtct ttgtcataac ccacaggtgt anaaacaagg 240
gtgcaacatg aaatttctgt ttcgtagcaa gtgcctgtct cacagttgtc aagtctgccc 300

```

310

<211> 370

<212> DNA

<213> Homo sapiens

<220>

```
<221> misc_feature
```

 $\langle 222 \rangle \quad (1) \dots (370)$

<223> n = A,T,C or G

<400> 424

gctcaaaaat	ctttttactg	ataggcatgg	ctacacaatc	attgactatt	agaggccaga	60
ggagaatgag	gcttggcctg	ggagccctgt	gcttactaga	agcacattag	attatccatt	120
cactgacaga	acagggtctt	tttgggtcct	tcttctccac	cacgatatac	ttgcagtcct	180
ccttcttgaa	gattcttttg	cagttgtctt	tgtcataacc	cacaggtgta	gaaacatcct	240
ggttgaatct	cctggaactc	cctcattagg	tatgaaatag	catgatgcat	tgcataaagt	300
cacgaaggtg	gcaaagatca	caacgctgcc	cagganaaca	ttcatttgtga	taagcaggac	360
tccgtcgacg						370

<210> 425

<211> 216

<212> DNA

<213> Homo sapiens

 $\langle 220 \rangle$

```
<221> misc_feature
```

 $\langle 222 \rangle \quad (1) \dots (216)$

<223> n = A, T, C or G

<400> 425

aattgctatn	ntttatntttg	ccactcaaaa	taattaccaa	aaaaaaaaaa	tnttaaataga	60
taacaacnca	acatcaagggn	aaananaaca	ggaatggntg	actntgcata	aatnggccga	120
anattatcca	ttatnttaag	ggttgacttc	aggntacagc	acacagacaa	acatgcccg	180
gaggntntca	ggaccgctcg	atgtntnttg	aggagg			216

<210> 426

<211> 596

<212> DNA

<213> Homo sapiens

<400> 426

cttcacagtga	ggataaacctt	gttgccccgg	gcgaggttc	tccattaggc	tctgattgat	60
tggcagtcag	tgatggaagg	gtgtttctgat	cattccgact	gccccaaagg	tgcgtggcca	120
gctctctgtt	ttgotgagtt	ggcagtagga	cctaatttgt	taattaagag	tagatgggtga	180
gctgtccttg	tatttttgatt	aacctaattg	ccttcccagc	acgactcgga	ttcagctgga	240
gacatcacgg	caacttttaa	tgaaatgatt	tgaagggccca	ttaagaggca	cttcccgtta	300
ttaggcagtt	catctgcact	gataactttct	tggcagctga	gctggtcgga	gctgtggccc	360
aaacgcacac	ttggcttttg	gttttgagat	acaactctta	atcttttagt	catgcttgag	420
ggtggaatggc	cttttcagct	ttaacccaat	ttgcactgcc	ttggaagtgt	agccaggaga	480

```
<210> 430
<211> 507
<212> DNA
<213> Homo sapiens
```

<220>
 <221> misc_feature
 <222> (1)...(507)
 <223> n = A,T,C or G

<400> 430
 cttatcncaa tggggctccc aaacttggct gtgcagtgga aactccgggg gaattttgaa 60
 gaacactgac acccatcttc caccgagaca ctctgattta attgggctgc agtgagaaca 120
 gagcatcaat ttaaaaaagct gcccgagaatg ttntcctggg cagcgttggtg atctttgccn 180
 ccttcgtgac tttatgcaat gcatcatgct atttcatacc taatgaggga gttccaggag 240
 attcaaccag gatgtttcta cncctgtggg ttatgacaaa gacaactgcc aaagaatntt 300
 caagaaggag gactgcaagt atatcgtggt ggagaagaag gacccaaaaa agacctgttc 360
 tgtcagtga tggataatct aatgtgcttc tagtaggcac agggctccca ggccaggcct 420
 cattctctc tggcctctaa tagtcaatga ttgtgtagcc atgcctatca gtaaaaagat 480
 ttttgagcaa aaaaaaaaaa aaaaaaa 507

<210> 431
 <211> 392
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(392)
 <223> n = A,T,C or G

<400> 431
 gaaaattcag aatggataaa aacaaatgaa gtacaaaata tttcagattt acatagcgat 60
 aaacaagaaa gcacttatca ggaggactta caaatggaag tacactctan aaccatcatc 120
 tatcatggct aaatgtgaga ttagcacagc tgtattattt gtacattgca aacacctaga 180
 aagagatggg aaacaaaatc ccaggagttt tgtgtgtgga gtccctgggtt ttccaacaga 240
 catcattcca gcattctgag attagggnga ttggggatca ttctggagtt ggaatgttca 300
 acaaaaagtga tgttgttagg taaaatgtac aacttctgga tctatgcaga cattgaaggt 360
 gcaatgagtc tggcttttac tctgctgttt ct 392

<210> 432
 <211> 387
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(387)
 <223> n = A,T,C or G

<400> 432
 ggtatccnta cataatcaaa tatagctgta gtacatgttt tcattggngt agattaccac 60
 aaatgcaagg caacatgtgt agatctcttg tcttattctt ttgtctataa tactgtattg 120
 ngtagtccaa gctctcggna gtccagccac tngnaaacat gctcccttta gattaacctc 180
 gtggacnctn ttgttgnatt gtctgaactg tagngccctg tattttgctt ctgtctgnga 240

```

attctgttgc ttctggggca tttccttgng atgcagagga ccaccacaca gatgacagca 300
atctgaattg ntccaatcac agctgcgatt aagacatact gaaatcgtac aggaccggga 360
acaacgtata gaacactgga gtccttt 387

```

<210> 433

<211> 281

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(281)

<223> n = A,T,C or G

<400> 433

```

ttcaactagc anagaanact gcttcagggg gtgtaaaatg aaaggcttcc acgcagttat 60
ctgattaaag aacactaaga gagggacaag gctagaagcc gcaggatgtc tacactatag 120
caggcnctat ttgggttggc tggaggagct gtggaaaaca tggagagatt ggcgctggag 180
atcgccgtgg ctattcctcn ttgntattac accagngagg ntctctgtnt gccactgggt 240
tnnaaaaccg ntatacaata atgatagaat aggacacaca t 281

```

<210> 434

<211> 484

<212> DNA

<213> Homo sapiens

<400> 434

```

ttttaaaata agcatttagt gctcagtcct tactgagtac tctttctctc cctcctctg 60
aatttaattc tttcaacttg caatttgcaa ggattacaca tttcactgtg atgtatattg 120
tgttgcaaaa aaaaaaaagt gtctttgttt aaaattactt ggtttgtaga tccatcttgc 180
tttttcccca ttggaactag tcattaaccc atctctgaac tggtagaaaa acatctgaag 240
agctagtcta tcagcatctg acaggtgaat tggatggttc tcagaaccat ttcaccaga 300
cagcctgttt ctatcctgtt taataaatta gtttggttct tctacatgca taacaaaccc 360
tgctccaatc tgtcacataa aagtctgtga cttgaagttt agtcagcacc cccaccaaac 420
tttatttttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataaag taccatgtc 480
ttta 484

```

<210> 435

<211> 424

<212> DNA

<213> Homo sapiens

<400> 435

```

gcgccgctca gagcagggtca ctttctgcct tccacgtcct ccttcaagga agcccatgt 60
gggtagcttt caatatcgca ggttcttact cctctgcctc tataagctca aaccaccaa 120
cgatcgggca agtaaacccc ctccctcgcc gacttcggaa ctggcgagag ttcagcgag 180
atgggcctgt ggggaggggg caagatagat gagggggagc ggcaggtgtc ggggtgacct 240
cttgagagaga ggaaaaaggc cacaagaggg gctgccaccg ccactaacgg agatggccct 300
ggtagagacc tttgggggtc tggaacctct ggactcccca tgctctaact cccacactct 360
gctatcagaa acttaaacctt gaggattttc tctgtttttc actcgcaata aattcagagc 420
aaac 424

```

<400> 438
ctgcttatca caatgaatgt tctcctgggc agcgttqtga tctttgccac ctctctgact 60

```

ttatgcaatg catcatgcta tttcatacct aatgagggag ttccaggaga ttcaaccagg 120
atgtttctac acctgtgggt tatgacaaag acaactgcc aagaatcttc aagaaggagg 180
actgcaagta tatctggtgg agaagaagga cccaaaaaag acctgttctg tcagtgaatg 240
gataatctaa tgtgcttcta gtaggcacag ggctcccagg ccaggcctca ttctcctctg 300
gcctctaata gtcaataatt gtgtagccat gcctatcagt aaaaagattt ttgagcaaac 360

```

<210> 439

<211> 431

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1) ... (431)

<223> n = A,T,C or G

<400> 439

```

gttcctnnta actcctgcc aaaacagctc tcctcaacat gagagctgca cccctcctcc 60
tgccaggggc agcaagcctt agccttggct tcttgtttct gctttttttc tggctagacc 120
gaagtgtact agccaaggag ttgaagtttg tgacttttgt gtttcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
gccaaactcac ccagctggggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attcttgaat gagtcctata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg agtgctatga caaacctggc agcccgtcga cgcggccgcg 420
aatttagtag t                                     431

```

<210> 440

<211> 523

<212> DNA

<213> Homo sapiens

<400> 440

```

agagataaag cttaggtcaa agttcataga gttcccatga actatatgac tggccacaca 60
ggatcttttg tatttaagga ttctgagatt ttgcttgagc aggattagat aaggctgttc 120
tttaaatgtc tgaaatggaa cagatttcaa aaaaaaacc cacaatctag ggtgggaaca 180
aggaagggaa gatgtgaata ggctgatggg caaaaaacca atttaccat cagttccagc 240
cttctctcaa ggagaggcaa agaaaggaga tacagtggag acatctggaa agttttctcc 300
actggaaaac tgctactatc tgtttttata tttctgttaa aatatatgag gctacagaac 360
taaaaattaa aacctctttg tgtcccttgg tcctggaaca tttatgttcc ttttaaagaa 420
acaaaaatca aactttacag aaagatttga tgtatgtaat acatatagca gctcttgaag 480
tatatatatc atagcaaata agtcatctga tgagaacaag cta                                     523

```

<210> 441

<211> 430

<212> DNA

<213> Homo sapiens

<400> 441

```

gttcctccta actcctgcc aaaacagctc tcctcaacat gagagctgca cccctcctcc 60
tgccaggggc agcaagcctt agccttggct tcttgtttct gctttttttc tggctagacc 120
gaagtgtact agccaaggag ttgaagtttg tgacttttgt gtttcggcat ggagaccgaa 180

```

```
<210> 442
<211> 362
<212> DNA
<213> Homo sapiens
```

```
<210> 443
<211> 624
<212> DNA
<213> Homo sapiens
```

<400>	443						
tttttttttt	gcaacacaat	atacatcaca	gtgaaatgtg	taatccttgc	aaattgcaag	60	
ttgaaagaat	taaattcaga	ggaggggaga	gaaagagtac	tcagtaggga	ctgagcacta	120	
aatgcttatt	ttaaagaaa	tgtaaagagc	agaaagcaat	tcaggctacc	ctgccttttg	180	
tgctggctag	tactccggtc	gggtgcagca	gcacgtggca	ttgaacattg	caatgtggag	240	
cccaaacacc	agaaaatggg	gtgaaattgg	ccaactttct	attaacttgg	cttcctgttt	300	
tataaaatat	tgtgaataat	atcacctact	tcaaagggca	gttatgaggc	ttaaatgaac	360	
taacgcctac	aaaacactta	aacatagata	acataggtgc	aagtactatg	tatctggtac	420	
atggtaaaca	tccttattat	taaagtcaac	gctaaaatga	atgtgtgtgc	atatgtcta	480	
agtacagaga	gagggcactt	aaaccaacta	agggcctgga	gggaagggtt	cctggaaaga	540	
ngatgcttgt	gctgggtcca	aatcttggtc	tactatgacc	ttggccaaat	tatttaaact	600	
ttgtccctat	ctqctaaaca	gatac				624	

```
<220>  
<221> misc_feature  
<222> (1)...(425)
```


<223> n = A,T,C or G

<400> 444

```
gcacatcatt nntcttgcatt tctttgagaa taagaagatc agtaaatagt tcagaagtgg 60
gaagctttgt ccaggcctgt gtgtgaaccc aatgttttgc ttagaaatag aacaagtaag 120
ttcattgcta tagcataaca caaaatttgc ataagtgggtg gtcagcaaatt ccttgaatgc 180
tgcttaaatgt gagaggttgg taaaatcctt tgtgcaaacac tctaactccc tgaatgtttt 240
gctgtgctgg gacctgtgca tgccagacaa ggccaagctg gctgaaagag caaccagcca 300
cctctgcaat ctgccacctc ctgctggcag gatttgtttt tgcactcctgt gaagagccaa 360
ggaggcacca gggcataagt gagtagactt atggctcgacg cggccgcgaa tttagtagta 420
gtaga 425
```

<210> 445

<211> 414

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(414)

<223> n = A,T,C or G

<400> 445

```
catgtttatg nttttggatt actttgggca cctagtgttt ctaaatcgtc tatcattctt 60
ttctgttttt caaaagcaga gatggccaga gtctcaacaa actgtatctt caagtctttg 120
tgaaattctt tgcattgtggc agattatttg atgtagtctt ctttaactag catataaatc 180
tgggtgtgtt cagataaatg aacagcaaaa tgtggtggaa ttaccatttg gaacattgtg 240
aatgaaaaat tgtgtctcta gattatgtaa caaataacta tttcctaacc attgatcttt 300
ggatttttat aatcctactc acaaatagact aggtctctcc tcttgtattt tgaagcagtg 360
tgggtgctgg attgataaaa aaaaaaaaaa tgcacgcggc cgcgaattta gtag 414
```

<210> 446

<211> 631

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(631)

<223> n = A,T,C or G

<400> 446

```
acaaattaga anaaagtgcc agagaacacc acataccttg tccggaacat tacaatggct 60
tctgcatgca tgggaagtgt gagcattcta tcaatatgca ggagccatct tgcagggtgtg 120
atgctggtta tactggacaa cactgtgaaa aaaaggacta cagtgttcta tacgttgttc 180
ccggtcctgt acgatttcag tatgtcttaa tgcagctgtg gattggaaca attcagattg 240
ctgtcatctg tgtggtgggc ctctgcatca caagggccaa actttaggta atagcattgg 300
actgagattt gtaaaccttc caacctcca ggaaatgccc cagaagcaac agaattcaca 360
gacagaagca aaatacaggg cactacagtt cagacaatac aacaagagcg tccacgaggt 420
taatctaaag ggagcatgtt tcacagtggc tggactaccg agagcttgga ctacacaata 480
cagtattata gacaaaagaa taagacaaga gatctacaca tgttgccttg catttgggtg 540
```

<400> 449
ccaagttcat gctntgtgct ggacgctgga cagggggcaa aagcnnnttgc tcgtqqqtca 60

```

ttctgancac cgaactgacc atgccagccc tgccgatggc cctccatggc tccctagtgc 120
cctggagagg aggtgtctag tcagagagta gtccctggaag gtggcctctg ngaggagcca 180
cggggacagc atcctgcaga tggtcgggcg cgtcccattc gccattcagg ctgcgcaact 240
gttgggaagg gcgatcggtg cgggcctctt cgctattacg ccagctggcg aaaggggggat 300
gtgctgcaag gcgattaagt tgggtaacgc cagggttttc ccagtcncga cgttgtaaaa 360
cgacggccag tgaattgaat ttaggtgacn ctatagaaga gctatgacgt cgcattgcacg 420
cgtacgtaag cttggatcct ctagagcggc cgcctactac tactaaattc gcggccgcgt 480
cgacgtggga tccnactga gagagtggag agtgacatgt gctggacnct gtccatgaag 540
cactgagcag aagctggagg cacaacgcnc cagacactca cagctactca ggaggctgag 600
aacaggttga acctgggagg tggaggttgc aatgagctga gatcaggccn ctgcncacca 660
gcatggatga cagagtgaaa ctccatctta aaaaaaaaaa aaaaaa 706

```

<210> 450

<211> 493

<212> DNA

<213> Homo sapiens

<400> 450

```

gagacggagt gtcactctgt tgcccaggct ggagtgcagc aagacactgt ctaagaaaaa 60
acagttttaa aaggtaaaac aacataaaaa gaaatatact atagtggaaa taagagagtc 120
aaatgaggct gagaacttta caaagggatc ttacagacat gtcgccaata tcaactgcatg 180
agcctaagta taagaacaac ctttggggag aaaccatcat ttgacagtga ggtacaattc 240
caagtcaggc agtgaaatgg gtggaattaa actcaaatta atcctgccag ctgaaacgca 300
agagacactg tcagagagtt aaaaagttag ttctatccat gaggtgattc cacagtcttc 360
tcaagtcaac acatctgtga actcacagac caagttctta aaccactgtt caaactctgc 420
tacacatcag aatcacctgg agagctttac aaactcccat tgccgagggt cgacgcggcc 480
gcgaatttag tag 493

```

<210> 451

<211> 501

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(501)

<223> n = A,T,C or G

<400> 451

```

gggcgcgtcc cattcgccat tcaggctgcg caactgttgg gaagggcgat cgggtgcgggc 60
ctcttcgcta ttacgccagc tggcgaaagg gggatgtgct gcaaggcgat taagttgggt 120
aacgccaggg ttttcccagt cncgacgttg taaaacgacg gccagtgaat tgaatttagg 180
tgacnctata gaagagctat gacgtgcgat gcacgcgtac gtaagcttgg atcctctaga 240
gcggccgcct actactacta aattcgcggc cgcgtcgacg tgggatccnc actgagagag 300
tggagagtga catgtgctgg acnctgtcca tgaagcactg agcagaagct ggaggcacia 360
cgcncagac actcacagct actcaggagg ctgagaacag gttgaacctg ggaggtggag 420
gttgcaatga gctgagatca ggccnctgcn ccccagcatg gatgacagag tgaaactcca 480
tcttaaaaaa aaaaaaaaaa a 501

```

<210> 452

<211> 51

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(51)

<223> n = A,T,C or G

<400> 452

agacgggtttc accnttacaa cnccttttag gatgggnntt ggggagcaag c 51

<210> 453

<211> 317

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(317)

<223> n = A,T,C or G

<400> 453

tacatcttgc tttttcccca ttggaactag tcattaaccc atctctgaac tggtagaaaa 60
 acatctgaag agctagtcta tcagcatctg gcaagtgaat tggatgggtc tcagaaccat 120
 ttcaccana cagcctgttt ctatcctgtt taataaatta gtttgggttc tctacatgca 180
 taacaaaccc tgctccaatc tgtcacataa aagtctgtga cttgaagttt antcagcacc 240
 cccaccaaac tttatttttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataagg 300
 taccatgtc tttatta 317

<210> 454

<211> 231

<212> DNA

<213> Homo sapiens

<400> 454

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 taagccacgc cacgctcttg aaggagtctt gaattctcct ctgctcactc agtagaacca 120
 agaagaccaa attcttctgc atcccagctt gcaaacaaaa ttgttcttct aggtctccac 180
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<210> 455

<211> 231

<212> DNA

<213> Homo sapiens

<400> 455

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 gtttcaacgc attgatgact tctccaagga tcttcctttg gcatcgacca cattcagggg 180
 caaagaattht ctcatagcac agtcacaaat acagggtctc tttctcctct a 231

<210> 456
 <211> 231
 <212> DNA
 <213> Homo sapiens

<400> 456
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 tgcactcaaa ttccctttatc aggaataaact acatagccac tatttacaaa gccattggaa 180
 cctttttatt tgggtgcagct gctagtcagt ccctgactga cattgccaag t 231

<210> 457
 <211> 231
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
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 <223> n = A,T,C or G

<400> 457
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 tatttgattt tattagcaat ctctttcaga agacccttga gatcattaag ctttgtatcc 180
 agttgtctaa atcgatgcct catttcctct gaggtgtcgc tggcttttgt g 231

<210> 458
 <211> 231
 <212> DNA
 <213> Homo sapiens

<400> 458
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 acaccctaac cttgggtaac agcatttgga attatcattt gggatgagta gaatttcaa 180
 ggtcctgggt taggcatttt gggggggccag accccaggag aagaagattc t 231

<210> 459
 <211> 231
 <212> DNA
 <213> Homo sapiens

<400> 459
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 gccctgact gttttccctc caccacagcc atcctgtccc tcattggctc tgtgctttcc 180
 actatacaca gtcaccgtcc caatgagaaa caagaaggag caccctccac a 231

<210> 460
 <211> 231

<212> DNA

<213> Homo sapiens

<400> 460

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cccacctccc cacacgcaca cggccagcct ggagcccaca gaagggtcct cctgcagcca 180
gtggagcttg gtccagcctc cagtccaccc ctaccaggct taaggataga a 231
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<210> 461

<211> 231

<212> DNA

<213> Homo sapiens

<400> 461

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gtgggggttca gtgaggagtg ggaaattggg tcagcagAAC caagccgttg ggtgaataag 180
agggggattc catggcactg atagagccct atagtttcag agctgggaat t 231
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<210> 462

<211> 231

<212> DNA

<213> Homo sapiens

<400> 462

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gaagaactgt tagagagacc aacagggtag tgggttagag atttcagag tcttacattt 180
tctagaggag gtatttaatt tcttctcact catccagtgt tgtatttagg a 231
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<210> 463

<211> 231

<212> DNA

<213> Homo sapiens

<400> 463

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catttgacag gtgtcttttc ctctggacct cgggtgtcccc atctgagtga gaaaaggcag 180
tggggaggtg gatcttccag tcgaagcggg atagaagccc gtgtgaaaag c 231
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<210> 464

<211> 231

<212> DNA

<213> Homo sapiens

<400> 464

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aaggacatca catatgaaga atgtttaagt tggaggtggc aacgtgaatt gcaaacaggg 120
cctgcttcag tgactgtgtg cctgtagtcc cagctactcg ggagtctgtg tgaggccagg 180
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ggtgccagcg caccagctag atgctctgta acttctagggc cccattttcc c 231

<210> 465

<211> 231

<212> DNA

<213> Homo sapiens

<400> 465

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aggatggcac aatttttggct tgtgttcata atatactcag attagttcag ctccatcaga 180
taaactggag acatgcagga cattagggta gtgttgtagc tctggtaatg a 231

<210> 466

<211> 231

<212> DNA

<213> Homo sapiens

<400> 466

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cctgtgcaat caaatattgt ggagaattcc ctagctggag aagtcacaaa gactataggc 180
aataatggag accagtccca caagatgaca accagtcgtt gtgtgcgggt g 231

<210> 467

<211> 311

<212> DNA

<213> Homo sapiens

<400> 467

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tgtgccttaa cagaaggctc tgagattcta agtgggaatc atttcagtga ctgtcatgtg 180
gcatgggtct ctgccaagc tctgaatgag actatagcaa ggcggctgtg ggacgtcagt 240
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<210> 468

<211> 3112

<212> DNA

<213> Homo sapiens

<400> 468

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 tttgtccttg tagttaattg aaagaaatag ggcactcttg tgagccactt tagggttcac 3060
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<210> 469

<211> 2229

<212> DNA

<213> Homo sapiens

<400> 469

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 aacgtgtccc ataaacattc cctctgtggc tcttgcatct catatattta tctaaactct 360
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 ggtcacctga ggtcaggagt tcaagaccag cctggccaat atggtgaaac cccatctcta 2160
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 aatggaatt 2229

<210> 470

<211> 2426

<212> DNA

<213> Homo sapiens

<400> 470

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 caaaattcta aagcgactc accatgaaat ggataaagggt tacctttggg gatttgcact 180
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 ccataaacat tccctctgtg gctcttgcac ttcatatatt tatctaaact cttataatca 360

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aattacactt ttagtatttg ctgtctcatg tgatgatgaa tctcatatgt gtcccttctt 420
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2426

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<210> 471

<211> 812

<212> DNA

<213> Homo sapiens

<400> 471

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gagatcagat attacaacag ctttgttttg agggttagaa atatgaaatg atttggttat 180
gaacgcacag tttaggcagc agggccagaa tcctgaccct ctgccccgtg gttatctcct 240
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acagggcgag gctcatcgat gacccaagat ggcggccggg catttctccc agggatctct 540

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gtgcttcctt ttgtgcttcc tgtgtgtgtg gatattttaa ggggctggaa atgtgcaaaa 600
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ccatttcagc agatgtgtgg cctcagatgg taaagtcagc agcctttctt atttctcacc 720
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<210> 472

<211> 515

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

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<223> n = A,T,C or G

<400> 472

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gaaaaaaaaa naaaaaaaaa aaanaaaaan aaaaa 515

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<210> 473

<211> 5829

<212> DNA

<213> Homo sapiens

<400> 473

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<211> 1594

<212> DNA

<213> Homo sapiens

<400> 474

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<211> 2414

<212> DNA

<213> Homo sapiens

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<223> n=A,T,C or G

<400> 475

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<211> 3434

<212> DNA

<213> Homo sapiens

<400> 476

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<210> 477
<211> 141
<212> PRT
<213> Homo sapiens

<400> 477
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Leu Ser His Tyr His Arg Asp Thr Arg His His Thr Val Thr Trp Thr
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His His His Thr His Glu His Thr Asp Thr Leu Pro Tyr Gly His Trp
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His Thr His Cys His Thr Val Thr Trp Thr His Leu His Thr Ile Thr
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Pro Pro His Thr Leu Pro Val Asp Thr Arg Thr His Arg His Cys His

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Pro	Pro	Leu	Trp	Cys	Arg	Leu	Asn	Tyr	Pro	Ala	Gly	Gly	Thr	Ala	Val		
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<210> 478

<211> 144

<212> PRT

<213> Homo sapiens

<400> 478

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<210> 479

<211> 223

<212> PRT

<213> Homo sapiens

<400> 479

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Ser His Glu His Thr Gly Ile Val Thr Trp Thr Asp Thr Gln Thr Tyr
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Gly Glu Ile Thr Leu Thr His His His Thr Ile Thr Gly Thr Gln Thr
              35              40              45

His Gly Asp Ile Thr Thr Trp Thr His Cys His Thr Thr Thr Gly Thr
              50              55              60

Arg Asp Ile Thr Leu Ser His Gly His Thr Ile Thr His Met Asn Thr
              65              70              75              80

Pro Thr His Cys His Met Asp Thr Ala Thr His Thr Ala Thr Leu Ser
              85              90              95

His Gly His Thr Ser Ile Pro Ser His His His Thr His Cys His Val
              100              105              110

Asp Thr Arg Thr His Arg His Cys His Thr Asp Thr Gln Asn Thr Val
              115              120              125

Thr Arg Arg His His His Ala Asp Thr Pro Pro His Gly His Ser Thr
              130              135              140

Arg His Ser Ala Thr Gln Ile His His His Thr Glu Met Arg Thr His
              145              150              155              160

Cys His Thr Asp Thr Thr Thr Ser Leu Pro His Phe His Val Ser Ala
              165              170              175

Gly Gly Val Gly Pro Thr Thr Leu Gly Ser Asn Arg Glu Ile Thr Trp
              180              185              190

Thr Tyr Ser Glu Gly Lys Ile Phe Phe Tyr Phe Leu Gly Asn Gln Ala
              195              200              205

Arg Leu Cys Leu Lys Lys Arg Lys Lys Lys Gln Tyr Thr Val
              210              215              220

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<210> 480

<211> 145

<212> PRT

<213> Homo sapiens

<400> 480

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Met Glu Pro Tyr Arg Gly Asn Glu Gln Pro Ser Gln Glu Gln Gly Val

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20					25					30						
Val	Gly	Phe	Leu	Val	Val	Lys	Arg	Gln	Thr	Ile	Gly	Arg	Leu	Glu	Arg	
35					40					45						
Asp	Phe	Met	Phe	Lys	Cys	Arg	Lys	Gln	Pro	Gly	Leu	Pro	Pro	Ser	Gly	
50					55					60						
Leu	Cys	Leu	Leu	Trp	Pro	Trp	Pro	Asn	Leu	Glu	Phe	Gly	Arg	Arg	Gln	
65					70					75					80	
Asp	Arg	Leu	Thr	Trp	Ser	Ser	Val	Ser	Val	Ala	Gly	Val	Cys	Ala	Cys	
85					90					95						
Arg	Ala	Arg	Pro	Gly	Trp	Leu	Gly	Glu	Gln	Pro	Ala	Thr	Ser	Ala	Gly	
100					105					110						
Val	Arg	Leu	Glu	Gln	Val	Glu	Gln	Pro	Pro	Ala	His	Pro	Leu	Gln	Glu	
115					120					125						
Ala	Gly	Val	Ala	Arg	Phe	Pro	Arg	Pro	Glu	Trp	Val	Pro	Pro	Asn	Gly	
130					135					140						

<210> 481

<211> 168

<212> PRT

<213> Homo sapiens

<400> 481

Met	His	Gly	Pro	Gln	Val	Leu	Ala	Arg	Cys	Ser	Glu	Cys	Ala	Cys	Pro	
5					10					15						
Ala	Leu	Ala	Ala	Thr	Ser	Ala	Gly	Val	Arg	Leu	Glu	Gly	Val	Asp	Arg	
20					25					30						
Pro	Pro	Thr	Leu	Pro	Ser	Gln	Gly	Ser	Gly	Trp	Pro	Cys	Ser	His	Ser	
35					40					45						
Leu	Ser	Gly	Cys	His	Leu	Met	Ala	Asp	Gly	Ala	Lys	Ala	Leu	Gly	Lys	
50					55					60						
Ala	Asp	Gly	Pro	Trp	Pro	Tyr	Leu	Phe	Val	Arg	Arg	Thr	Asp	Val	Pro	
65					70					75					80	

Cys Pro Ala Ala Ser Glu Val Gly Gly Cys Ala Pro Ser Ser Trp Arg
 85 90 95
 Ala Leu Ala Glu Val Thr Gly Cys Ser Leu Gly Pro Leu Gly Leu Ala
 100 105 110
 Gln His Ala Gln Ala Ser Val Leu Leu Leu Cys Tyr Lys Trp Ser His
 115 120 125
 Ile Gly Glu Thr Ser Ser His Leu Arg Ser Lys Val Tyr Ala Ala Phe
 130 135 140
 Gly Gly Ser Ser Pro Cys Leu Lys Gly Leu Met Ser Leu Trp Ala Ser
 145 150 155 160
 Trp Leu Ser Arg Gly Arg Pro
 165

<210> 482

<211> 144

<212> PRT

<213> Homo sapiens

<400> 482

Met Glu Pro Tyr Arg Gly Asn Lys Lys Gln Val Gln Glu Lys Gly Val
 5 10 15
 Pro Cys Leu Trp Gly Ser Ser Pro Cys Leu Arg Cys His Met Ala Leu
 20 25 30
 Arg Ala Ser Trp Leu Pro Gly Gly Gly Pro Gln Ala Ile Leu Gly Arg
 35 40 45
 Thr Leu Cys Ser Ser Ala Glu Ser Ser Gln Asp Cys His Pro Gly Gly
 50 55 60
 Pro Ser Ile Ala Leu Ala Lys Pro Cys Arg Gly Val Trp Leu Leu Phe
 65 70 75 80
 Glu Pro Ala Trp Pro Pro Trp His Ala Arg Ala Pro Gly Ala Gly Thr
 85 90 95
 Leu Leu Arg Val Cys Leu Ser Cys Leu Gly Cys His Leu Cys Gly Gly
 100 105 110
 Ala Ser Gly Gly Gly Gly Pro Ala Thr Asn Leu Thr Gln Ser Arg Lys
 115 120 125
 Trp Met Ala Met Phe Pro Gln Pro Glu Trp Leu Pro Pro Asp Gly
 130 135 140

<210> 490
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 490
 Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala Gly Ala Thr Cys
 1 5 10 15
 Leu Ser His Ser
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<210> 491
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 491
 Thr Cys Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala Ala Leu
 1 5 10 15
 Thr Gly Phe Thr
 20

<210> 492
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 492
 Ala Leu Thr Gly Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr
 1 5 10 15
 Leu Ala Ser Leu
 20

<210> 493
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 497
 Leu Leu Pro Pro Pro Pro Ala Leu Cys Gly Ala Ser Ala Cys Asp Val
 1 5 10 15
 Ser Val Arg Val
 20

<210> 498
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 498
 Asp Val Ser Val Arg Val Val Val Gly Glu Pro Thr Glu Ala Arg Val
 1 5 10 15
 Val Pro Gly Arg
 20

<210> 499
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 499
 Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile Leu Asp
 1 5 10 15
 Ser Ala Phe Leu
 20

<210> 500
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 500
 Leu Asp Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met

1 5 10 15
 Gly Ser Ile Val
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 <210> 501
 <211> 20
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Made in a lab
 <400> 501
 Phe Met Gly Ser Ile Val Gln Leu Ser Gln Ser Val Thr Ala Tyr Met
 1 5 10 15
 Val Ser Ala Ala
 20

<210> 502
 <211> 414
 <212> DNA
 <213> Homo Sapien

<400> 502
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 ctgtagagtt tttggaatng acctcagtag caatgcaatg agctgggtcc gccaggctcc 180
 agggaagggg ctggaatgga tcggagccat tgataattgt ccacantacg cgacctgggc 240
 gaaaggccga ttnatnattt ccaaaacctn gaccacggtg gatttgaaaa tgaccagtcc 300
 gacaaccgag gacacggcca cctatTTTTg tggcagaatg aatactggta atagtgggtg 360
 gaagaatatt tggggcccag gcaccctggt caccgtntcc tcagggcaac ctaa 414

<210> 503
 <211> 379
 <212> DNA
 <213> Homo Sapien

<400> 503
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 agctatggag tgagctgggt ccgccaggct ccagggaagg ggctgggnata catcgatca 180
 ttagtagtag tgggtacattt tacgcgagct gggcgaaagg ccgattcacc atttccaaaa 240
 cctngaccac ggtggatttg aaaatcacca gtttgacaac cgaggacacg gccacctatt 300
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 tntccttagg gcaacctaa 379

<210> 504
 <211> 19
 <212> PRT
 <213> Artificial Sequence

<223> Made in a lab

Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp Ser Pro Tyr Phe Lys Glu
1 5 10 15
Asn Ser Ala

<213> Artificial Sequence

<223> Made in a lab

Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn Asp Asn Val Thr
 1 5 10 15
 Asn Thr Ala Asn
 20

<213> Homo Sapien

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tcgctggagg	agtcggggg	tcgcctggtc	acgcctggga	cacccctgac	actcacctgc	120
accgtctctg	gattctccct	cagtagcaat	gcaatgatct	gggtccgcc	ggctccaggg	180
aaggggctgg	aatacatcgg	atacattagt	tatggtggta	gcgcatacta	cgcgagctgg	240
gtgaaaggcc	gattcaccat	ctccaaaacc	tcgaccacgg	tggatctgag	aatgaccagt	300
ctgacaaccg	aggacacggc	cacctatttc	tgtgccagaa	atagtgattt	tagtggtagt	360
ttgtggggcc	caggcaccct	ggtcaccgtc	tcctcagggc	aacctaa		407

<213> Homo Sapien

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acagtctctg	gattctccct	cagcaactac	gacctgaact	gggtccgcca	ggctccaggg	180
aaggggctgg	aatggatcgg	gatcattaat	tatgttggtg	ggacggacta	cgcgaactgg	240
gcaaaaaggcc	ggttcaccat	ctccaaaacc	tcgaccaccg	tggatctcaa	gatcgccagt	300
ccgacaaccg	aggacacggc	cacctatttc	tgtgccagag	ggtggaagtg	cgatgagtct	360
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422

<400> 508

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<220>
<223> Made in a lab
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<400> 509

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<220>
<223> Made in a lab
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<400> 510

<220>
<223> Made in a lab

<400> 511

Tyr His Pro Ser Met Phe Cys Ala Gly Gly Gly Gln Asp Gln Lys

1 5 10 15

<210> 512
 <211> 15
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 512

Asp Ser Gly Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu
 1 5 10 15

<210> 513
 <211> 15
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 513

Ala Pro Cys Gly Gln Val Gly Val Pro Asx Val Tyr Thr Asn Leu
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<210> 514
 <211> 15
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 514

Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
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<210> 515
 <211> 15
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 515

Met Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg
 1 5 10 15

<210> 516

<211> 15
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 516
 Val Ser Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln
 1 5 10 15

<210> 517
 <211> 15
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 517
 Glu Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met
 1 5 10 15

<210> 518
 <211> 15
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 518
 Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg His Tyr Asp Glu Gly
 1 5 10 15

<210> 519
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 519
 Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg Asn Tyr Asp Glu Gly Cys
 1 5 10 15
 Gly

<210> 520
 <211> 25

<212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 520
 Val Gly Glu Gly Leu Tyr Gln Gly Val Pro Arg Ala Glu Pro Gly Thr
 1 5 10 15
 Glu Ala Arg Arg His Tyr Asp Glu Gly
 20 25

<210> 521
 <211> 21
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 521
 Ala Pro Phe Pro Asn Gly His Val Gly Ala Gly Gly Ser Gly Leu Leu
 1 5 10 15
 Pro Pro Pro Pro Ala
 20

<210> 522
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 522
 Leu Leu Val Val Pro Ala Ile Lys Lys Asp Tyr Gly Ser Gln Glu Asp
 1 5 10 15
 Phe Thr Gln Val
 20

<210> 523
 <211> 254
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Made in a lab

<400> 523
 Met Ala Thr Ala Gly Asn Pro Trp Gly Trp Phe Leu Gly Tyr Leu Ile
 1 5 10 15

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Leu Gly Val Ala Gly Ser Leu Val Ser Gly Ser Cys Ser Gln Ile Ile
 20 25 30
 Asn Gly Glu Asp Cys Ser Pro His Ser Gln Pro Trp Gln Ala Ala Leu
 35 40 45
 Val Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln
 50 55 60
 Trp Val Leu Ser Ala Thr His Cys Phe Gln Asn Ser Tyr Thr Ile Gly
 65 70 75 80
 Leu Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met
 85 90 95
 Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu
 100 105 110
 Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu
 115 120 125
 Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala
 130 135 140
 Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg
 145 150 155 160
 Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu
 165 170 175
 Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys
 180 185 190
 Ala Gly Gly Gly Gln Xaa Gln Xaa Asp Ser Cys Asn Gly Asp Ser Gly
 195 200 205
 Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly
 210 215 220
 Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu
 225 230 235 240
 Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
 245 250

<210> 524

<211> 765

<212> DNA

<213> Homo sapien

<400> 524

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tcgcagccct ggcaggcggc actggtcatg gaaaacgaat tgttctgctc gggcgtcctg      180
gtgcatccgc agtgggtgct gtcagccgca cactgtttcc agaactccta caccatcggy      240
ctgggcctgc acagtcttga ggccgaccaa gagccaggga gccagatggt ggaggccagc      300
ctctccgtac ggcacccaga gtacaacaga cccttgctcg ctaacgacct catgctcatc      360
aagttaggacg aatccgtgtc cgagtctgac accatccgga gcatcagcat tgcttcgcag      420
tgccctaccg cggggaactc ttgcctcggt tctggctggg gtctgctggc gaacggcaga      480
atgcctaccg tgctgcagtg cgtgaacgtg tcgggtggtg ctgaggaggt ctgcagtaag      540
ctctatgacc cgctgtacca cccagcatg ttctgcgccg gcggagggca agaccagaag      600
gactcctgca acggtgactc tggggggccc ctgatctgca acgggtactt gcagggcctt      660
gtgtctttcg gaaaagcccc gtgtggccaa gttggcgtgc caggtgtcta caccaacctc      720
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<210> 525
 <211> 254
 <212> PRT
 <213> Homo sapien

<400> 525
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 20 25 30
 Asn Gly Glu Asp Cys Ser Pro His Ser Gln Pro Trp Gln Ala Ala Leu
 35 40 45
 Val Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln
 50 55 60
 Trp Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly
 65 70 75 80
 Leu Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met
 85 90 95
 Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu
 100 105 110
 Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu
 115 120 125
 Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala
 130 135 140
 Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg
 145 150 155 160
 Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu
 165 170 175
 Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys
 180 185 190
 Ala Gly Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly
 195 200 205
 Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly
 210 215 220
 Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu
 225 230 235 240
 Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
 245 250

<210> 526
 <211> 963
 <212> DNA
 <213> Homo sapiens

<400> 526
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 aactgcatcg tgggtcttcat cgtaaggacg gaacgcagcc tgcacgctcc gatgtacctc 180
 tttctctgca tgcttgcagc cattgacctg gccttatcca catccaccat gcctaagatc 240
 cttgcccttt tctgggtttga ttcccgagag attagctttg aggcctgtct taccagatg 300
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cgttatgtgg ccactctgcc cccactgcgc catgctgcag tgetcaacaa tacagtaaca 420
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ctgatcaagc ggctggcctt ctgccactcc aatgtcctct cgcactccta ttgtgtccac 540
caggatgtaa tgaagtgggc ctatgcagac actttgcccc atgtggtata tgggtcttact 600
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tga

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<210> 527

<211> 321

<212> PRT

<213> Homo sapiens

<400> 527

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Met Ser Ser Cys Asn Phe Thr His Ala Thr Phe Val Leu Ile Gly Ile
                5                      10                      15

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```

Pro Gly Leu Glu Lys Ala His Phe Trp Val Gly Phe Pro Leu Leu Ser
                20                      25                      30

```

```

Met Tyr Val Val Ala Met Phe Gly Asn Cys Ile Val Val Phe Ile Val
                35                      40                      45

```

```

Arg Thr Glu Arg Ser Leu His Ala Pro Met Tyr Leu Phe Leu Cys Met
                50                      55                      60

```

```

Leu Ala Ala Ile Asp Leu Ala Leu Ser Thr Ser Thr Met Pro Lys Ile
                65                      70                      75                      80

```

```

Leu Ala Leu Phe Trp Phe Asp Ser Arg Glu Ile Ser Phe Glu Ala Cys
                85                      90                      95

```

```

Leu Thr Gln Met Phe Phe Ile His Ala Leu Ser Ala Ile Glu Ser Thr
                100                      105                      110

```

```

Ile Leu Leu Ala Met Ala Phe Asp Arg Tyr Val Ala Ile Cys His Pro
                115                      120                      125

```

```

Leu Arg His Ala Ala Val Leu Asn Asn Thr Val Thr Ala Gln Ile Gly
                130                      135                      140

```

```

Ile Val Ala Val Val Arg Gly Ser Leu Phe Phe Phe Pro Leu Pro Leu
                145                      150                      155                      160

```

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Leu Ile Lys Arg Leu Ala Phe Cys His Ser Asn Val Leu Ser His Ser
                165                      170                      175

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Tyr Cys Val His Gln Asp Val Met Lys Leu Ala Tyr Ala Asp Thr Leu
180 185 190

Pro Asn Val Val Tyr Gly Leu Thr Ala Ile Leu Leu Val Met Gly Val
195 200 205

Asp Val Met Phe Ile Ser Leu Ser Tyr Phe Leu Ile Ile Arg Thr Val
210 215 220

Leu Gln Leu Pro Ser Lys Ser Glu Arg Ala Lys Ala Phe Gly Thr Cys
225 230 235 240

Val Ser His Ile Gly Val Val Leu Ala Phe Tyr Val Pro Leu Ile Gly
245 250 255

Leu Ser Val Val His Arg Phe Gly Asn Ser Leu His Pro Ile Val Arg
260 265 270

Val Val Met Gly Asp Ile Tyr Leu Leu Leu Pro Pro Val Ile Asn Pro
275 280 285

Ile Ile Tyr Gly Ala Lys Thr Lys Gln Ile Arg Thr Arg Val Leu Ala
290 295 300

Met Phe Lys Ile Ser Cys Asp Lys Asp Leu Gln Ala Val Gly Gly Lys
305 310 315 320

<210> 528

<211> 20

<212> DNA

<213> Homo Sapien

<400> 528

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<210> 529

<211> 20

<212> DNA

<213> Homo Sapien

<400> 529

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20

<210> 530

<211> 1852

<212> DNA

<213> Homo sapiens

<400> 530

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gtggcgctga tggctgagga cagagcttca gtgtggcttc tctgogactg gcttcttcgg 420
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<211> 879

<212> DNA

<213> Homo sapiens

<400> 531

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<212> DNA
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<211> 267
<212> PRT
<213> Homo sapiens

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Leu Gln Ser Met Pro Gln Gly Ser Tyr Ala Thr Ala Arg Phe Leu Val
      35              40              45
Ala Lys Arg Pro Thr Thr Gly His Leu Glu Lys Glu Phe Met Phe His

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 65 70 75 80
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 Ser Ser Val Leu Val Pro Gln Ile Cys Ala Cys Gln Thr Arg Pro Asn
 100 105 110
 Trp Leu Asn Glu Gln Pro Ala Thr Ser Ala Gly Val Arg Leu Glu Glu
 115 120 125
 Val Asp Gln Pro Pro Thr Leu Pro Ser Gln Gly Ser Gly Trp Pro Cys
 130 135 140
 Ser His Ser Leu Ser Gly Cys His Leu Met Ala Asp Ile Ala Lys Ala
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 Leu Gly Lys Ala Asp Gly Pro Trp Pro Tyr Leu Phe Val Arg Arg Thr
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 Asp Val Pro Cys Pro Ala Ala Ser Glu Val Gly Gly Cys Ala Pro Ser
 180 185 190
 Ser Trp His Thr Leu Ala Glu Val Thr Gly Cys Ser Leu Ser Pro Leu
 195 200 205
 Ser Leu Ala Gln His Ala Gln Ala Ser Val Leu Leu Leu Cys Tyr Lys
 210 215 220
 Trp Ser His Ile Gly Glu Thr Ser Ser His Leu Arg Ser Lys Val Tyr
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 <212> DNA
 <213> Homo sapiens

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<211>	6140

<213> Homo sapiens

<221> unsure

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<211> 1229

<212> PRT

<213> Homo sapiens

<400> 537

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Ile Gly His Lys Arg Arg Leu Glu Glu Asp Asp Met Tyr Ser Val Leu
35 40 45

Pro Glu Asp Arg Ser Gln His Leu Gly Glu Glu Leu Gln Gly Phe Trp
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Asp Lys Glu Val Leu Arg Ala Glu Asn Asp Ala Gln Lys Pro Ser Leu
65 70 75 80

Thr Arg Ala Ile Ile Lys Cys Tyr Trp Lys Ser Tyr Leu Val Leu Gly
85 90 95

Ile Phe Thr Leu Ile Glu Glu Ser Ala Lys Val Ile Gln Pro Ile Phe
100 105 110

Leu Gly Lys Ile Ile Asn Tyr Phe Glu Asn Tyr Asp Pro Met Asp Ser
115 120 125

Val Ala Leu Asn Thr Ala Tyr Ala Tyr Ala Thr Val Leu Thr Phe Cys
130 135 140

Thr Leu Ile Leu Ala Ile Leu His His Leu Tyr Phe Tyr His Val Gln
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Cys Ala Gly Met Arg Leu Arg Val Ala Met Cys His Met Ile Tyr Arg
165 170 175

Lys Ala Leu Arg Leu Ser Asn Met Ala Met Gly Lys Thr Thr Thr Gly

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Val Thr Ala Leu Leu Trp Met Glu Ile Gly	Ile Ser Cys Leu Ala Gly	
225	230	235
Met Ala Val Leu Ile Ile Leu Leu Pro	Leu Gln Ser Cys Phe Gly Lys	
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Leu Phe Ser Ser Leu Arg Ser Lys Thr	Ala Thr Phe Thr Asp Ala Arg	
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Ile Arg Thr Met Asn Glu Val Ile Thr Gly	Ile Arg Ile Ile Lys Met	
275	280	285
Tyr Ala Trp Glu Lys Ser Phe Ser Asn Leu	Ile Thr Asn Leu Arg Lys	
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Lys Glu Ile Ser Lys Ile Leu Arg Ser Ser	Cys Leu Arg Gly Met Asn	
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Gln Leu Pro Ser Asp Gly Lys Lys Met Val	His Val Gln Asp Phe Thr	
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Ala Phe Trp Asp Lys Ala Ser Glu Thr Pro	Thr Leu Gln Gly Leu Ser	
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Phe Thr Val Arg Pro Gly Glu Leu Leu Ala	Val Val Gly Pro Val Gly	
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0022330-00250900

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Gly Asp Arg Gly Thr	Thr Leu Ser Gly Gly	Gln Lys Ala Arg	Val Asn	
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Leu Ala Arg Ala Val	Tyr Gln Asp Ala Asp	Ile Tyr Leu Leu	Asp Asp	
	545	550	560	
Pro Leu Ser Ala Val	Asp Ala Glu Val Ser	Arg His Leu Phe	Glu Leu	
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Cys Ile Cys Gln Ile	Leu His Glu Lys Ile	Thr Ile Leu Val	Thr His	
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Gln Leu Gln Tyr Leu	Lys Ala Ala Ser Gln	Ile Leu Ile Leu	Lys Asp	
	595	600	605	
Gly Lys Met Val Gln	Lys Gly Thr Tyr Thr	Glu Phe Leu Lys	Ser Gly	
	610	615	620	
Ile Asp Phe Gly Ser	Leu Leu Lys Lys Asp	Asn Glu Glu Ser	Glu Gln	
	625	630	640	
Pro Pro Val Pro Gly	Thr Pro Thr Leu Arg	Asn Arg Thr Phe	Ser Glu	
	645	650	655	
Ser Ser Val Trp Ser	Gln Gln Ser Ser Arg	Pro Ser Leu Lys	Asp Gly	
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Ala Leu Glu Ser Gln	Asp Thr Glu Asn Val	Pro Val Thr Leu	Ser Glu	
	675	680	685	
Glu Asn Arg Ser Glu	Gly Lys Val Gly Phe	Gln Ala Tyr Lys	Asn Tyr	
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Phe Arg Ala Gly Ala	His Trp Ile Val Phe	Ile Phe Leu Ile	Leu Leu	
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Thr	Ile	Arg	Ala	Tyr	Lys	Ala	Glu	Glu	Arg	Cys	Gln	Glu	Leu	Phe	Asp	
Ala	His	Gln	Asp	Leu	His	Ser	Glu	Ala	Trp	Phe	Leu	Phe	Leu	Thr	Thr	
Ser	Arg	Trp	Phe	Ala	Val	Arg	Leu	Asp	Ala	Ile	Cys	Ala	Met	Phe	Val	
Ile	Ile	Val	Ala	Phe	Gly	Ser	Leu	Ile	Leu	Ala	Lys	Thr	Leu	Asp	Ala	
Gly	Gln	Val	Gly	Leu	Ala	Leu	Ser	Tyr	Ala	Leu	Thr	Leu	Met	Gly	Met	
Phe	Gln	Trp	Cys	Val	Arg	Gln	Ser	Ala	Glu	Val	Glu	Asn	Met	Met	Ile	

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          995              1000              1005
Ser Val Glu Arg Val Ile Glu Tyr Thr Asp Leu Glu Lys Glu Ala Pro
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Trp Glu Tyr Gln Lys Arg Pro Pro Pro Ala Trp Pro His Glu Gly Val
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Ile Ile Phe Asp Asn Val Asn Phe Met Tyr Ser Pro Gly Gly Pro Leu
          1045              1050              1055

Val Leu Lys His Leu Thr Ala Leu Ile Lys Ser Gln Glu Lys Val Gly
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Ile Val Gly Arg Thr Gly Ala Gly Lys Ser Ser Leu Ile Ser Ala Leu
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Phe Arg Leu Ser Glu Pro Glu Gly Lys Ile Trp Ile Asp Lys Ile Leu
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Thr Thr Glu Ile Gly Leu His Asp Leu Arg Lys Lys Met Ser Ile Ile
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Pro Gln Glu Pro Val Leu Phe Thr Gly Thr Met Arg Lys Asn Leu Asp
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Pro Phe Asn Glu His Thr Asp Glu Glu Leu Trp Asn Ala Leu Gln Glu
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Val Gln Leu Lys Glu Thr Ile Glu Asp Leu Pro Gly Lys Met Asp Thr
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Glu Leu Ala Glu Ser Gly Ser Asn Phe Ser Val Gly Gln Arg Gln Leu
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Val Cys Leu Ala Arg Ala Ile Leu Arg Lys Asn Gln Ile Leu Ile Ile
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<400> 538
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Asp	Pro	Met	Asp	Ser	Val	Ala	Leu	Asn	Thr	Ala	Tyr	Ala	Tyr	Ala	Thr	
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Phe	Tyr	His	Val	Gln	Cys	Ala	Gly	Met	Arg	Leu	Arg	Val	Ala	Met	Cys	
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Lys	Thr	Thr	Thr	Gly	Gln	Ile	Val	Asn	Leu	Leu	Ser	Asn	Asp	Val	Asn	
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Lys	Phe	Asp	Gln	Val	Thr	Val	Phe	Leu	His	Phe	Leu	Trp	Ala	Gly	Pro	
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Thr	Asn	Leu	Arg	Lys	Lys	Glu	Ile	Ser	Lys	Ile	Leu	Arg	Ser	Ser	Cys	
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Ala	Ser	Arg	Val	Phe	Val	Ala	Val	Thr	Leu	Tyr	Gly	Ala	Val	Arg	Leu
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Thr	Val	Thr	Leu	Phe	Phe	Pro	Ser	Ala	Ile	Glu	Arg	Val	Ser	Glu	Ala
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Ile	Val	Ser	Ile	Arg	Arg	Ile	Gln	Thr	Phe	Leu	Leu	Leu	Asp	Glu	Ile
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Ser	Gln	Arg	Asn	Arg	Gln	Leu	Pro	Ser	Asp	Gly	Lys	Lys	Met	Val	His
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Val	Gln	Asp	Phe	Thr	Ala	Phe	Trp	Asp	Lys	Ala	Ser	Glu	Thr	Pro	Thr
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Val	Gly	Pro	Val	Gly	Ala	Gly	Lys	Ser	Ser	Leu	Leu	Ser	Ala	Val	Leu
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Gly	Glu	Leu	Ala	Pro	Ser	His	Gly	Leu	Val	Ser	Val	His	Gly	Arg	Ile
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Ala	Tyr	Val	Ser	Gln	Gln	Pro	Trp	Val	Phe	Ser	Gly	Thr	Leu	Arg	Ser
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Lys	Ala	Arg	Val	Asn	Leu	Ala	Arg	Ala	Val	Tyr	Gln	Asp	Ala	Asp	Ile
		500						505				510			
Tyr	Leu	Leu	Asp	Asp	Pro	Leu	Ser	Ala	Val	Asp	Ala	Glu	Val	Ser	Arg
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His	Leu	Phe	Glu	Leu	Cys	Ile	Cys	Gln	Ile	Leu	His	Glu	Lys	Ile	Thr
530						535				540					
Ile	Leu	Val	Thr	His	Gln	Leu	Gln	Tyr	Leu	Lys	Ala	Ala	Ser	Gln	Ile

	820		825		830	
Ile Phe Leu Arg Arg Tyr Phe Leu Glu Thr Ser Arg Asp Val Lys Arg						
	835		840		845	
Leu Glu Ser Thr Thr Arg Ser Pro Val Phe Ser His Leu Ser Ser Ser						
	850		855		860	
Leu Gln Gly Leu Trp Thr Ile Arg Ala Tyr Lys Ala Glu Glu Arg Cys						
	865		870		875	880
Gln Glu Leu Phe Asp Ala His Gln Asp Leu His Ser Glu Ala Trp Phe						
		885		890		895
Leu Phe Leu Thr Thr Ser Arg Trp Phe Ala Val Arg Leu Asp Ala Ile						
		900		905		910
Cys Ala Met Phe Val Ile Ile Val Ala Phe Gly Ser Leu Ile Leu Ala						
		915		920		925
Lys Thr Leu Asp Ala Gly Gln Val Gly Leu Ala Leu Ser Tyr Ala Leu						
		930		935		940
Thr Leu Met Gly Met Phe Gln Trp Cys Val Arg Gln Ser Ala Glu Val						
		945		950		955
Glu Asn Met Met Ile Ser Val Glu Arg Val Ile Glu Tyr Thr Asp Leu						
			965		970	975
Glu Lys Glu Ala Pro Trp Glu Tyr Gln Lys Arg Pro Pro Pro Ala Trp						
		980		985		990
Pro His Glu Gly Val Ile Ile Phe Asp Asn Val Asn Phe Met Tyr Ser						
		995		1000		1005
Pro Gly Gly Pro Leu Val Leu Lys His Leu Thr Ala Leu Ile Lys Ser						
		1010		1015		1020
Gln Glu Lys Val Gly Ile Val Gly Arg Thr Gly Ala Gly Lys Ser Ser						
	1025		1030		1035	1040
Leu Ile Ser Ala Leu Phe Arg Leu Ser Glu Pro Glu Gly Lys Ile Trp						
		1045		1050		1055
Ile Asp Lys Ile Leu Thr Thr Glu Ile Gly Leu His Asp Leu Arg Lys						
		1060		1065		1070
Lys Met Ser Ile Ile Pro Gln Glu Pro Val Leu Phe Thr Gly Thr Met						
		1075		1080		1085
Arg Lys Asn Leu Asp Pro Phe Asn Glu His Thr Asp Glu Glu Leu Trp						

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 Asn Ala Leu Gln Glu Val Gln Leu Lys Glu Thr Ile Glu Asp Leu Pro
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 Gly Lys Met Asp Thr Glu Leu Ala Glu Ser Gly Ser Asn Phe Ser Val
 1125 1130 1135
 Gly Gln Arg Gln Leu Val Cys Leu Ala Arg Ala Ile Leu Arg Lys Asn
 1140 1145 1150
 Gln Ile Leu Ile Ile Asp Glu Ala Thr Ala Asn Val Asp Pro Arg Thr
 1155 1160 1165
 Asp Glu Leu Ile Gln Lys Lys Ile Arg Glu Lys Phe Ala His Cys Thr
 1170 1175 1180
 Val Leu Thr Ile Ala His Arg Leu Asn Thr Ile Ile Asp Ser Asp Lys
 1185 1190 1195 1200
 Ile Met Val Leu Asp Ser Gly Arg Leu Lys Glu Tyr Asp Glu Pro Tyr
 1205 1210 1215
 Val Leu Leu Gln Asn Lys Glu Ser Leu Phe Tyr Lys Met Val Gln Gln
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002290-002290

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Ala Val Val Thr Ala Ser Ala Ala Leu

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<211> 14

<212> PRT

<213> Homo sapiens

<400> 541

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<211> 15

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Thr Gln Val Val Phe Asp Lys Ser Asp Leu Ala Lys Tyr Ser Ala

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<211> 12

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Phe Met Gly Ser Ile Val Gln Leu Ser Gln Ser Val

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<210> 544

<211> 18

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Thr Tyr Val Pro Pro Leu Leu Leu Glu Val Gly Val Glu Glu Lys Phe

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Met Thr

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<211> 18

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<213> Homo sapiens

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Met Asp Arg Leu Val Gln Arg Phe Gly Thr Arg Ala Val Tyr Leu Ala
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Ser Val

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<211> 29

<212> PRT

<213> Homo sapiens

<400> 546

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Thr Glu Ala Arg Arg His Tyr Asp Glu Gly Val Arg Met
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<210> 547

<211> 58

<212> PRT

<213> Homo sapiens

<400> 547

Val Ala Glu Glu Ala Ala Leu Gly Pro Thr Glu Pro Ala Glu Gly Leu
 5 10 15

Ser Ala Pro Ser Leu Ser Pro His Cys Cys Pro Cys Arg Ala Arg Leu
 20 25 30

Ala Phe Arg Asn Leu Gly Ala Leu Leu Pro Arg Leu His Gln Leu Cys
 35 40 45

Cys Arg Met Pro Arg Thr Leu Arg Arg Leu
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<210> 548

<211> 18

<212> PRT

<213> Homo sapiens

<400> 548

Ile Asp Trp Asp Thr Ser Ala Leu Ala Pro Tyr Leu Gly Thr Gln Glu
 5 10 15

Glu Cys

<210> 549

<211> 18

<212> PRT

<213> Homo sapiens

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Leu Glu Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro Asp His Cys Arg
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Gln Ala

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Asn His Pro Glu Gln Gly Ser Ser Thr Pro Arg Pro Gln Thr His Thr
 5 10 15

Ser Pro Arg Thr Ile Met Asn His Thr Thr Gln Glu Glu Val Ser Thr
 20 25 30

Arg Gln Ala Lys Glu Ala Ser Pro Val Leu Thr Ala Thr Arg His Gly
 35 40 45

Ser Tyr Tyr Ser Leu Asn Ser Ala Ser Thr Gln Ile Ser Asp Asn Ile
 50 55 60

Arg Asn Ser Leu Glu His Glu Pro Cys Cys Glu Leu Pro Ile Arg Arg
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Ile

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<211> 54

<212> PRT

<213> Homo sapiens

<400> 557

Ser Leu Ser Ala Thr Pro Leu Thr Leu Trp Asn Ser Ser Asp Pro Leu
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Glu Gln Ala Tyr Leu Ile Ser Ala Arg Glu Lys Thr Asn Asn Gly Leu
 20 25 30

Lys Gly Ser Leu Thr Met Lys Val Ser Ala Asn Ser Trp Leu Arg Cys
 35 40 45

Gly Phe His Ile Arg Phe
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<211> 77

<212> PRT

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<222> (1)...(77)

<223> Xaa = Any amino acid

<400> 558

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55

<210> 561

<211> 57

<212> PRT

<213> Homo sapiens

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<222> (1)...(57)

<223> Xaa = Any amino acid

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Gly	Leu	Lys	Ser	Pro	Glu	Ile	Lys	Asn	Pro	Ala	Pro	Thr	Gly	Thr	Ser
			20					25					30		

Asn	Leu	Ser	Cys	Phe	Leu	Ser	Xaa	Phe	Trp	Leu	Met	Gln	Gly	Thr	Asn
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Ser	Leu	Pro	Arg	Glu	Asn	Tyr	Leu	Asn
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<211> 59

<212> PRT

<213> Homo sapiens

<220>

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<222> (1)...(59)

<223> Xaa = Any amino acid

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Ala	Pro	Met	His	Gly	Ile	Lys	Asn	Ser	Ile	Thr	Ser	Leu	Ile	Phe	Leu
			20					25					30		

Ile	Ser	Tyr	Leu	Xaa	Leu	Glu	Met	Ser	Ser	Leu	Ser	Glu	Ser	Leu	Val
		35					40					45			

Leu	Ser	Ser	Gly	Asp	Tyr	Val	Leu	Asp	Thr	Pro
	50							55		

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 <211> 79
 <212> PRT
 <213> Homo sapiens

<400> 563
 Cys Phe Leu Phe Pro Tyr Leu Trp Leu Tyr Ala Gln Pro Leu Phe Pro
 5 10 15
 Lys Gln Gln Pro Pro Ala Leu Ala Pro Gly His Pro Asp Phe Ile His
 20 25 30
 Thr Gln Asn Glu Gln Ile Asp Pro Ser Pro His Ile Gln Asn Leu Met
 35 40 45
 Trp Asn Pro His Leu Ser Gln Glu Leu Ala Glu Thr Phe Met Val Arg
 50 55 60
 Asp Pro Leu Arg Pro Leu Leu Val Phe Ser Leu Ala Asp Ile Arg
 65 70 75

<210> 564
 <211> 64
 <212> PRT
 <213> Homo sapiens

<400> 564
 Ala Cys Ser Lys Gly Ser Glu Glu Phe Gln Arg Val Arg Gly Val Ala
 5 10 15
 Glu Arg Asp Gln Cys Leu Phe Leu Leu Leu Cys Tyr Gln Ile Tyr Thr
 20 25 30
 Val Arg His Leu Tyr Ile Leu Tyr Arg Thr Leu Gly Ser Arg Lys Ser
 35 40 45
 His Met Asn Leu Pro Leu Ser Ser Gly Ser Gln Leu Trp Leu Ala Pro
 50 55 60

<210> 565
 <211> 57
 <212> PRT
 <213> Homo sapiens

<220>
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 <222> (1)...(57)
 <223> Xaa = Any amino acid

<400> 565

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 5 10 15

Ala Val Cys Cys Gly Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln
 20 25 30

Asn Ile Asp Val Ser Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu
 35 40 45

Tyr Ala Val Ser Ser Xaa His Asn Val
 50 55

<210> 566

<211> 55

<212> PRT

<213> Homo sapiens

<400> 566

Ile Leu Leu Glu Phe Phe Arg Asn Gln Arg Gly Ser Leu Asn Pro Arg
 5 10 15

Lys Thr Val Pro Phe Ile Lys Ser Glu Gly Gly Glu Lys Lys Gly His
 20 25 30

Cys Asn His Ser Val Val Ser Ile Asp Ser Ala Ala Ala Leu Leu Pro
 35 40 45

Leu Lys Leu Val Leu Leu Pro
 50 55

<210> 567

<211> 51

<212> PRT

<213> Homo sapiens

<400> 567

Tyr Ser Asp Phe Asp Val Phe Cys Ser His Thr Tyr Gly Tyr Met Leu
 5 10 15

Ser His Cys Ser Gln Ser Ser Ser Pro Leu Leu Trp Pro Leu Gly Ile
 20 25 30

Leu Thr Leu Ser Thr His Lys Met Ser Lys Leu Thr Leu Pro Pro Ile
 35 40 45

Phe Arg Thr
 50


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<211> 951

<212> DNA

<213> Homo sapiens

<400> 570

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ccatttttagt actatgggtg agtacatgga attgaagtct ggcttaaate ttcagaaagt 180
tatatatcta ttttatttta tttttttgag acagagtctc gctgtgtcac ccaggctgga 240
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<210> 571

<211> 819

<212> DNA

<213> Homo sapiens

<400> 571

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<212> PRT
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<210> 579

<211> 57

<212> PRT

<213> Homo sapiens

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Leu Tyr Ile Arg His His Asp Ser Gln Ser Phe Val Ile Leu Tyr Tyr
 20 25 30

Lys Lys Leu Asn Tyr Tyr Phe Lys Tyr Gly Gln Ile Arg Ala Phe His
 35 40 45

Ile Ala Lys Val Tyr Gln Pro His
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<210> 580

<211> 68

<212> PRT

<213> Homo sapiens

<400> 580

Met Glu Leu Arg Thr Lys Ala Leu Arg Thr Ala Gln Gln Leu Thr Ser
 5 10 15

Cys Val Thr Ala Leu Lys Ala Ala Gly Pro Pro Leu Thr Phe Trp Lys
 20 25 30

Gly Lys Trp Val Gln Cys Cys Leu Pro Leu Trp Gly Leu Leu Gly Ser
 35 40 45

His Ala Phe Tyr Ile Tyr Ala Val Asp Ile Phe Met Phe Pro Gly Ser
 50 55 60

Phe Ile His
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<210> 581

<211> 78

<212> PRT

<213> Homo sapiens

<400> 581

Met Leu Glu Val Lys Phe Glu Val Ser Leu Arg Pro Thr Gly Asn Glu
 5 10 15

30

Asp Gly Tyr Met Glu Pro Cys Phe Gln Leu Leu Phe
50 55 60

<213> Homo sapiens

ctggacactt	tgcgagggt	tttgtgtgct	gtgtgtgtgt	ccgctcatgc	tactcatcgt	60
agcccgcccg	gtgaagctcg	ctgctttccc	tacctcctta	agtgaactgc	aaacgcccac	120
cggctggaat	tgtcttggtt	atgatgacag	agaaaatgat	ctcttcctct	gtgacaccaa	180
cacctgtaaa	tttgatgggg	aatgtttaag	aattggagac	actgtgactt	gcgtctgtca	240
gttcaagtgc	aacaatgact	atgtgcctgt	gtgtggctcc	aatggggaga	gtaccagaaa	300
tgagtgttac	ctgcgacagg	ctgcatgcaa	acagcagagt	gagatacttg	tgggtgtcaga	360
aggatcatgt	gccacagatg	caggatcagg	atctggagat	ggagtccatg	aaggctcttg	420
agaaactagt	caaaaggaga	catccacctg	tgatatttgc	cagtttggtg	cagaatgtga	480
cgaagatgcc	gaggatgtct	ggtgtgtgtg	taatattgac	tgttctcaaa	ccaacttcaa	540
tcccctctgc	gcttctgatg	ggaaatctta	tgataatgca	tgccaaatca	aagaagcatc	600
gtgtcagaaa	caggagaaaa	ttgaagtcac	gtctttgggt	cgatgtcaag	ataacacaac	660
tacaactact	aagtctgaag	atgggcatta	tgcaagaaca	gattatgcag	agaatgctaa	720
caaatagaaa	gaaagtgcc	gagaacacca	cataccttgt	ccggaacatt	acaatggctt	780
ctgcatgcac	gggaagtgtg	agcattctat	caatatgcag	gagccatctt	gcagggtgtga	840
tgctggttat	actggacaac	actgtgaaaa	aaaggactac	agtgttctat	acgttgttcc	900
cggctcctgta	cgatttcagt	atgtcttaac	cgcagctgtg	attggaacaa	ttcagattgc	960
tgtcatctgt	gtggtggtcc	tctgcatcac	aaggaaatgc	cccagaagca	acagaattca	1020
cagacagaag	caaaatacag	ggcactacag	ttcagacaat	acaacaagag	cgtccacgag	1080
gttaatctaa	agggagcatg	tttcacagtg	gctggactac	cgagagcttg	gactacacaa	1140
tacagtatta	tagacaaaag	aataagacaa	gagatctaca	catgttgctt	tgcattttgtg	1200
gtaatctaca	ccaatgaaaa	catgtactac	agctatattt	gattatgtat	ggatataattt	1260
gaaatagtat	acattgtctt	gatgtttttt	ctgtaatgta	aataaactat	ttatatcaca	1320
caatawagtt	ttttctttcc	catgtatttg	ttatatataa	taaatactca	gtgatgagaa	1380
aaaaaaaaaa	aaaaaaaaaa	rwmgacc				1408

<213> Homo sapiens

Leu Gln Phe Arg Gln Tyr Asn Lys Ser Val His Glu Val Asn Leu Lys
20 25 30

Gly Ala Cys Phe Thr Val Ala Gly Leu Pro Arg Ala Trp Thr Thr Gln
 35 40 45

Tyr Ser Ile Ile Asp Lys Arg Ile Arg Gln Glu Ile Tyr Thr Cys Cys
 50 55 60

Leu Ala Phe Val Val Ile Tyr Thr Asn Glu Asn Met Tyr Tyr Ser Tyr
 65 70 75 80

Ile

<210> 589

<211> 157

<212> PRT

<213> Homo sapiens

<400> 589

Met Thr Met Cys Leu Cys Val Ala Pro Met Gly Arg Ala Thr Arg Met
 5 10 15

Ser Val Thr Cys Asp Arg Leu His Ala Asn Ser Arg Val Arg Tyr Leu
 20 25 30

Trp Cys Gln Lys Asp His Val Pro Gln Met Gln Asp Gln Asp Leu Glu
 35 40 45

Met Glu Ser Met Lys Ala Leu Glu Lys Leu Val Lys Arg Arg His Pro
 50 55 60

Pro Val Ile Phe Ala Ser Leu Val Gln Asn Val Thr Lys Met Pro Arg
 65 70 75 80

Met Ser Gly Val Cys Val Ile Leu Thr Val Leu Lys Pro Thr Ser Ile
 85 90 95

Pro Ser Ala Leu Leu Met Gly Asn Leu Met Ile Met His Ala Lys Ser
 100 105 110

Lys Lys His Arg Val Arg Asn Arg Arg Lys Leu Lys Ser Cys Leu Trp
 115 120 125

Val Asp Val Lys Ile Thr Gln Leu Gln Leu Leu Ser Leu Lys Met Gly
 130 135 140

Ile Met Gln Glu Gln Ile Met Gln Arg Met Leu Thr Asn
 145 150 155

<210> 590

<211> 347

<212> PRT

<213> Homo sapiens

<400> 590

Met Leu Leu Ile Val Ala Arg Pro Val Lys Leu Ala Ala Phe Pro Thr
 5 10 15

Ser Leu Ser Asp Cys Gln Thr Pro Thr Gly Trp Asn Cys Ser Gly Tyr
 20 25 30

Asp Asp Arg Glu Asn Asp Leu Phe Leu Cys Asp Thr Asn Thr Cys Lys
 35 40 45

Phe Asp Gly Glu Cys Leu Arg Ile Gly Asp Thr Val Thr Cys Val Cys
 50 55 60

Gln Phe Lys Cys Asn Asn Asp Tyr Val Pro Val Cys Gly Ser Asn Gly
 65 70 75 80

Glu Ser Tyr Gln Asn Glu Cys Tyr Leu Arg Gln Ala Ala Cys Lys Gln
 85 90 95

Gln Ser Glu Ile Leu Val Val Ser Glu Gly Ser Cys Ala Thr Asp Ala
 100 105 110

Gly Ser Gly Ser Gly Asp Gly Val His Glu Gly Ser Gly Glu Thr Ser
 115 120 125

Gln Lys Glu Thr Ser Thr Cys Asp Ile Cys Gln Phe Gly Ala Glu Cys
 130 135 140

Asp Glu Asp Ala Glu Asp Val Trp Cys Val Cys Asn Ile Asp Cys Ser
 145 150 155 160

Gln Thr Asn Phe Asn Pro Leu Cys Ala Ser Asp Gly Lys Ser Tyr Asp
 165 170 175

Asn Ala Cys Gln Ile Lys Glu Ala Ser Cys Gln Lys Gln Glu Lys Ile
 180 185 190

Glu Val Met Ser Leu Gly Arg Cys Gln Asp Asn Thr Thr Thr Thr Thr
 195 200 205

Lys Ser Glu Asp Gly His Tyr Ala Arg Thr Asp Tyr Ala Glu Asn Ala
 210 215 220

Asn Lys Leu Glu Glu Ser Ala Arg Glu His His Ile Pro Cys Pro Glu
 225 230 235 240

His Tyr Asn Gly Phe Cys Met His Gly Lys Cys Glu His Ser Ile Asn
245 250 255

Met Gln Glu Pro Ser Cys Arg Cys Asp Ala Gly Tyr Thr Gly Gln His
260 265 270

Cys Glu Lys Lys Asp Tyr Ser Val Leu Tyr Val Val Pro Gly Pro Val
275 280 285

Arg Phe Gln Tyr Val Leu Ile Ala Ala Val Ile Gly Thr Ile Gln Ile
290 295 300

Ala Val Ile Cys Val Val Val Leu Cys Ile Thr Arg Lys Cys Pro Arg
305 310 315 320

Ser Asn Arg Ile His Arg Gln Lys Gln Asn Thr Gly His Tyr Ser Ser
325 330 335

Asp Asn Thr Thr Arg Ala Ser Thr Arg Leu Ile
340 345

<210> 591

<211> 565

<212> DNA

<213> Homo sapien

<400> 591

actaaagcaa	atgaacaagc	tgacttgcta	gtatcatctg	cattcattga	agcacaagaa	60
cttcatgcct	tgactcatgt	aaatgcaata	ggattaaaaa	ataaatttga	tatcacatgg	120
aaacagacaa	aaaatattgt	acaacattgc	acccagtgtc	agattctaca	cctggccact	180
caggaagcaa	gagttaatcc	cagaggtcta	tgtcctaata	tgttatggca	aatggatgtc	240
atgcacgtac	cttcatttgg	aaaattgtca	tttgtccatg	tgacagttga	tacttattca	300
catttcataat	gggcaacctg	ccagacagga	gaaagtactt	cccatgttaa	aagacattta	360
ttatcttggt	ttcctgtcat	gggagttcca	gaaaaagtta	aaacagacaa	tgggccaggt	420
tactgtagta	aagcatttca	aaaattctta	aatcagtgga	aaattacaca	tacaatagga	480
attctctata	attcccaagg	acaggccata	attgaaggaa	ctaatagaac	actcaaagct	540
caattgggta	aacaaaaaaaa	aaaaa				565

<210> 592

<211> 188

<212> PRT

<213> Homo sapien

<400> 592

Thr	Lys	Ala	Asn	Glu	Gln	Ala	Asp	Leu	Leu	Val	Ser	Ser	Ala	Phe	Ile
1			5					10					15		
Glu	Ala	Gln	Glu	Leu	His	Ala	Leu	Thr	His	Val	Asn	Ala	Ile	Gly	Leu
			20				25				30				
Lys	Asn	Lys	Phe	Asp	Ile	Thr	Trp	Lys	Gln	Thr	Lys	Asn	Ile	Val	Gln

```

      35              40              45
His Cys Thr Gln Cys Gln Ile Leu His Leu Ala Thr Gln Glu Ala Arg
      50              55              60
Val Asn Pro Arg Gly Leu Cys Pro Asn Val Leu Trp Gln Met Asp Val
      65              70              75              80
Met His Val Pro Ser Phe Gly Lys Leu Ser Phe Val His Val Thr Val
      85              90              95
Asp Thr Tyr Ser His Phe Ile Trp Ala Thr Cys Gln Thr Gly Glu Ser
      100             105             110
Thr Ser His Val Lys Arg His Leu Leu Ser Cys Phe Pro Val Met Gly
      115             120             125
Val Pro Glu Lys Val Lys Thr Asp Asn Gly Pro Gly Tyr Cys Ser Lys
      130             135             140
Ala Phe Gln Lys Phe Leu Asn Gln Trp Lys Ile Thr His Thr Ile Gly
      145             150             155             160
Ile Leu Tyr Asn Ser Gln Gly Gln Ala Ile Ile Glu Gly Thr Asn Arg
      165             170             175
Thr Leu Lys Ala Gln Leu Val Lys Gln Lys Lys Lys
      180             185

```

<210> 593

<211> 271

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(271)

<223> n = A,T,C or G

<400> 593

```

actttatgtt cnagtgcana aanccnctg gattgccacc ntactctcag ggctgtgant      60
tgtgcnccca nagcaacctg ggcacgcggg gacagggggg ccnacaattg agggagcggg      120
gtccctagct ggggtctata catgncnggg naagggcngc tgagtnccat nagcaaagga      180
nctagnatnt gcgggggtgc ggccctgggcc taccctttna agcatccntn gatccactcc      240
angaanccng gggtagncag gtttnccaac a                                     271

```

<210> 594

<211> 376

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(376)

<223> n = A,T,C or G

<400> 594

```

cctttggggg nggggggaac ctttaccatt gtncctcttt atttcatttg gttnggggttc      60
gcgccctcnn gggccaacaa agttatcgtn nttgaagaga anattttttt ggnttngncc      120
cgattaagcg ncaaatgtgt agcaaaaangc cgtgccactt gtggcgtagc tncgtcgggt      180

```

```
<210> 595
<211> 242
<212> DNA
<213> Homo sapien
```

<400>	595						
agnctgctgn	tcgtnccctn	tatgtggctt	catnntgagg	acaanagtn	g	g	60
tgngnatgcc	aggcaaggnc	aagctggctc	aaaaagcatc	caccacctc	tgnaanggg	g	120
atgccangag	cangtgcacc	agtcccaact	angagncccn	ggcatgntac	atcttcttcc		180
accctnaaa	ntttgngcta	caangnccat	ttttcttttt	ctcttaaggg	ncnctggct		240
tc							242

```
<220>
<221> misc_feature
<222> (1) ... (535)
<223> n = A,T,C or G
```

```
<210> 597
<211> 257
<212> DNA
<213> Homo sapien
```

```
<220>  
<221> misc_feature  
<222> (1)...(257)
```

<223> n = A,T,C or G

<400> 597

tttcnataacc	caaaantacc	ccatattang	accanacatt	tgtctnggaa	aaattaccat	60
tntntaacnt	ttgggccacc	tgagannaaa	tgggtgtaat	ncatgataag	atggancagn	120
attnctctta	agatnngatn	agaccccggt	tttcacggaa	catatccaag	nacccaatag	180
gnaacaagcc	acgggnggag	tcacaaacat	atattcttta	ctctcataat	ccgtmncaca	240
naactnttgn	acttgac					257

<210> 598

<211> 222

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(222)

<223> n = A,T,C or G

<400> 598

nntggntacc	gtcnaaactt	nncttggtac	ccgagctcgg	atccactagt	ccagtgtggt	60
ggaattccat	tgtgttgggc	tataagctgt	aatagtggag	ncgtgctngg	ttcattgcan	120
nagnccctcc	gcanncacnc	ttggnacaac	ctgtgagnag	gcnataaatc	atccacataa	180
tcatactgc	atgaanctga	ctcaaacgca	tccacntaca	cc		222

<210> 599

<211> 238

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(238)

<223> n = A,T,C or G

<400> 599

gcatgacatc	ancgatgtnt	ttggnnacct	ganattngct	aaaactngng	natgccgggn	60
atgnagggtt	ggtantgatc	tatgcactca	catctcatgg	ggacgtttca	tgtggagtgn	120
tcgacaangt	tgctgnancn	gagaagtgat	gatctcagtt	gaaaggggtca	tgtgaataca	180
cnttacactt	gaaaaagaag	cacattggga	atatcacgaa	acgnccacca	acatcctg	238

<210> 600

<211> 232

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(232)

<223> n = A,T,C or G

<400> 600

cgaactat	ttt	agactaccta	ggaaaattat	tttagtatca	gaagaatatc	aggggtgtag	60
tactcatcag	agctaaatga	gagcgccttta	aaaatgttag	tttgtcttcc	gccatttcta		120
cagaaagctg	caatttcagg	ttttcaacct	aataggtgat	atttaanaaa	aaaaaaaagc		180
aatcgcaaat	agccccactg	cttttacaaa	tcattttttc	cccaacacaa	tg		232

<210> 601

<211> 547

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(547)

<223> n = A,T,C or G

<400> 601

cattgtgttg	gggaaaaaat	gatttgtata	agcagtgggg	ctatttgcca	ttgctttttt	60
tttttcttaa	atatcaccta	ttaggttgaa	aacctgaaat	tgcagctttc	tgtagaaatg	120
gcggaagaca	aactaacatt	tttaaagcgc	tctcatttag	ctctgatgag	tactacaccc	180
ctnatattct	tctgatacta	aaataatttt	cctagtgtag	tctaaacttt	tttaaaaaga	240
catgtaatcc	gcggagttag	taactcaaaa	cgagtgcac	tnggaagtat	cgcagccggt	300
nctggatnaa	attcccagct	tgctngcttg	ctnagccggg	gggcggtnaa	aaaaacatct	360
gcagcccngg	ggnaaaaacc	ttcgcatgtg	tcttacgtgt	ttacgttatt	ttatttcctt	420
nnagcaaggc	nggganttgg	ggactcgaaa	tggtacagtt	gggctgggga	tcgcccttgt	480
tacataaaaag	ncgtccagaa	gagggacggt	tacaggcngg	ganctccaaa	ggtcagtcct	540
tgccatt						547

<210> 602

<211> 826

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(826)

<223> n = A,T,C or G

<400> 602

cgggggggnt	tacgtctctc	tggacgcttt	tattgtacca	gggcgatccc	agcccaactg	60
taccattcga	gtccctactc	ctgccttget	ctagggaaat	aaaataacgt	aaacacgtaa	120
gaacaatgcg	aaagcgTTTT	cttccctagg	ctgcagattg	tcttcttcac	cgccccgtgt	180
tagctagcta	gctagctggg	aatttaatcc	agaaacggct	tgcgatacct	cctagatgca	240
ctcgTTTTga	gttacaaaact	cgcgggatta	catgtctttt	taaaaaagtt	tagactacac	300
tagggaaaaat	tatttttagta	tcagaagaat	atcagggggt	gtagtactca	tcagagctna	360
atgagagcgc	tttaaaaaatg	ttagtttgtc	ttccgccatt	tctacagaaa	gctgcaattt	420
caggTTTTca	ncctaatagg	tgatatntaa	gaaaaaaaaa	acaatcgcan	atagcccact	480
gcttttacaa	atcattttttc	tcttctaggt	atagcctgtc	aggtggccta	atgtattttt	540
gacatctcta	ggaatttttaa	tagaccagaa	atgggtgcc	gagatatgcc	tgactaatc	600
ttaagtgggg	atttatgtat	ttctcaanca	agtgattaaa	gcaaaaactag	gcacgaatga	660
aatcaagatc	tttaggccag	aaatcatgaa	nanttttana	attattttan	gaatctgtgg	720


```

cttctcttct taaaatngaa aaaaaaattg tttaaaccce naaggtctga ataccceagc 780
nccctgaach anagaacaan gccggagcac cccctcccaa atcccc 826

```

<210> 603

<211> 817

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (817)

<223> n = A,T,C or G

<400> 603

```

nnangacttt tgtggtntta tacaattntt ttttctattt ctatgaagag aaagccacag 60
agtcctaaaa taattctaaa actcatcatg actttcttgc ctaaaagatc ttgatttcaa 120
tcgtgcctag ttttgcttta atcacttgct tgagaaatac ataaatcccc acttaagatt 180
agtgacagga tatctctggc acccatttct gggtctatta aaattcctag agatgtcaaa 240
aattacatta ggccacctga caggctatac ctagaagaga aaaaatgatt tgtaaaagca 300
gtggggctat ttgcgattgc tttttttttt tcttaaatat cacctattag gttgaaaacc 360
tgaaattgca gctttctgta gaaatggcgg aagacaaact aacattttta aagcgtctct 420
atthagctct gatgagtact acacccctga tattcttctg atactaaaat aattttccta 480
gtgtagtcta aactttttta aaaagacatg taatccgagg agtttgtaac tcaaaacgag 540
tgcatctagg aggtatcgca agccgtttct ggattaaatt cccagctagc ttgcttgctt 600
agcaggggcy ggnaaanaag acatctgcag cctagggaag aaaacctttc gcattgttct 660
tacgtgttta cgttatttta tttcctanaa caaggcngaa ttgggactcg aatgggtcag 720
ttgggggtgg ggatcccctg gtncataaaa ngtcanaaag anggtacagg cggaacncca 780
agggtcgtcc tgcatttana ctcggaattt tgggtgcc 817

```

<210> 604

<211> 694

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (694)

<223> n = A,T,C or G

<400> 604

```

cttttcaaat catttttnct cttctaggta tancctgtca ggtggcctaa tgtaattttt 60
gacatctcta ngaattttta tagaaccaga aatgggtgcc agagatatgc ctgcactaat 120
cttaagtggg gatttatgta tttctcaagc aagtgattaa agcaaaacta ggcacgattg 180
aatcaagat ctttttaggca anaaagtcac gatgagtttt agaattatth taggactctg 240
tggctttctc ttcatagaaa tagaaaaaaa aattgtataa aaccacaaaa ggtcctgaat 300
agccaaagca acactganca aaaagaacan agcaggggaag caacacacta ccngaattca 360
aattatacta ccagggtgta gtaaccacaaa cagcattcta ttggcataaa atagacacca 420
agaccaatgg ancagaataa agaacccccc aaataaatcc atatatntac cgccanctga 480
ttatcaataa cnaacaccaa gaacatatnt taagggaant nctattcaat aantagtgtc 540
ggnaaaaaact gggaaatcca tatgcagaaa naatgaaact agacccttat ccctcaccat 600
acgcaaannt caacttcgga atgggattac aaaacttaag acattccaac ccaagaaact 660

```


<220>

<223> Primer

<400> 612

gcacatgggtt cactgcccc gcttttgccc cctgtccagc

40

<210> 613

<211> 38

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 613

gccgctcgag ttagaattcg gggttggcca cgatgggtg

38

<210> 614

<211> 53

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 614

cggcgggcat atgcatcacc atcaccatca catcataaac ggcgaggact gca

53

<210> 615

<211> 46

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 615

gcactcccag cctcccacaa tactggcctg gacggttttc tctatc

46

<210> 616

<211> 1350

<212> DNA

<213> Homo sapien

<400> 616

atgcatcacc	atcaccatca	catcataaac	ggcgaggact	gcagcccgca	ctcgcagccc	60
tggcaggcgg	cactgggtcat	ggaaaacgaa	ttgtttctgt	cgggcgtcct	ggtgcatccg	120
cagtgggtgc	tgtcagccgc	acactgtttc	cagaactcct	acaccatcgg	gctgggcctg	180
cacagtcttg	aggccgacca	agagccaggg	agccagatgg	tggaggccag	cctctccgta	240
cggcaccag	agtacaacag	acccttgctc	gctaacgacc	tcatgctcat	caagttggac	300


```

aaangctcan gcagcccggc tggccgcgcg cgctcctccc cccaggaaag ccaangtggg 120
ngctgatgtg gctgcangag ctcgtttcac agccctcan gtgganctgg ttgggcccgcg 180
gctgccangg gcggaagtgg gtgtcccan gtctcagccc caaggctgcc cctcaciaag 240
cactggtggt ttgcctccac tgccaccttg ggctccgaac ccgctcccct gctgtggang 300
cccaccgtgg gaatccaggt ccccaggtgg actgcctgcc ttgccctcac tgcccactct 360
gcccacactt ccctgcctag anaccgggaa ggggctgtgt cgggtantggg gcccacctgg 420
atgtggcagc accgactgtg ggggtggacc tggccttgcc ggggtgcaaaa gtggggggccc 480
ngggaaaagc acctgaagtg gccctgaaaa atccccctt aatttttccc caatttgggg 540
ctcnaacaaa aggaaattgc tgaagccaan ggtaccaagg tcacccttaa ggccagggtg 600
aaaagggtccc aaaattccaa tnccacacnt ttgggcttnc ctcttggaac cccggccccc 660
tctcntgaan ttttaaaaaa n 681

```

<210> 624

<211> 661

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(661)

<223> n = A,T,C or G

<400> 624

```

attggtctta ctgtaccacc ggggtgaaat cgatggccgc ggcgctctaaa tatccgattt 60
tttttttttt tcctcttctg actgtccatg gacaaatgaa actaacttaa tctaactaaa 120
aaacacaact atattttgaa gattttctat ctgcactcaa ggacactttc cacnccggtg 180
ttgttacctt ttggtcttgt ctctgaacat gaaattnatc tcaagggatt ngatttctgg 240
acctcctatt cctgctatgg gtttgatatt tcttgggctc cagggccact gttgcattgg 300
gntgacagnt acctcctagc ccatanctc ctatcttggg aaacaaacct aacaactacg 360
tgtaccttcc atagatctct gattgagtct cagtatnccg ctgctcatgg gcgattcact 420
tgaatccgtn attggtgcca acaatcctga ctcatggggnn aatggatcct atcacgttcc 480
cctgattngc aaccctgtg tacatanatc taatcgcata gaatctagcn tnggntatgc 540
gcggctacgc tatcagggnt tgntaactat ngcatggcta cgaancctga tcatgatcna 600
gggtcatgga ctcttatcag ggggggttggg ccgngcttct ttttcnnacc ttggtaaaac 660
c 661

```

<210> 625

<211> 181

<212> DNA

<213> Homo sapien

<400> 625

```

gcaacaatca gatcatgtta aagtaaactc ccattgccct ggatcacttc aggatttaat 60
tgtccaagga gagcagggtt ctctgtgtaa aaaaagggtg ggaaatgttt gagagtaaaa 120
aatacaaaat tcaaccgggtc gaaaatacac cactccattc agtgctctac ccccataagc 180
c 181

```

<210> 626

<211> 181

<212> DNA

<213> Homo sapien

```

<400> 626
gcaacaatca gatcatgtta aagtaaatct ccattgccct ggatcacttc aggatttaat      60
tgtccaagga gagcagggtt ctctgtgaa aaaaagggtg ggaaatgttt gagagtaaaa      120
aatacaaaat tcaaccggtc gaaaatacac cactccattc agtgctctac ccccataagc      180
c                                                                181

```

```

<210> 627
<211> 813
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(813)
<223> n = A,T,C or G

```

```

<400> 627
accaagctgg agctcgcgcg cctgcaggtc gacactagtg gatccaaagt gaacgtgaag      60
gtgagcagag gagaacttgc gatggcaaag ttaaaaacaa gaggagatga tggctcttgg      120
gtggcacagg atgttaaaaa aattctcctg tccttaagga gttactgcta tttgagtaat      180
gtgccacttc cctacatagc cttctatgca gaaatgctat atttccactt cacaaccag      240
aacgtgcatt ttattttaca tttagaggag gaacaaacaa ccagaaggca aaaactgggtg      300
cattattttt tgcaattctc ttggaaagag ttcgttttta acttctgctc agacagcaca      360
caactactgg gaatatattt taatttcaaa tctgatgtgt gacatctggg aactcattta      420
ttgctaatag agttttcaca ggaagcagca gtcaccagta gctcatctta tttttcagtt      480
ggcaaagtgt tgtttacctt ttattggcct gcacgggtgt ctcttatcac aggatattta      540
attagaaaac gcaagtagcc taacatagaa nagaaatgga gtggtagata atagtagata      600
gaatggctaa atatttttat tacagtgatg taatatcact gnaatttatg gttaaaaatt      660
atgtaatact caaaaggaat tctcagactg gogaaacagc tggncacag ctntcacagg      720
gctttanact cctnttgagc tttccccctg ntggacttta gtcttccttt tacncccgna      780
gttnccattn nttaccaatt gtnccgggaa ana                                                                813

```

```

<210> 628
<211> 646
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(646)
<223> n = A,T,C or G

```

```

<400> 628
tttggngnngn ggtgtctcnt ttgggtggac tttttgggtc gtagggcccc aaggccgtta      60
atcccgtaat aacggaagac gaagaagagt cagaagagtg cttctataag gatcgggacg      120
agactacctt agaggaataa aggaaaaaag cagaggagga agagtggtag aaggagtcag      180
aagaaacca cagctcgttc tgaacctgga gccttatcaa aaaggctctag ataaacgata      240
gcgatctcga tatcgagctc aagaggtagg tttagagact tctcgtcctc gagagcgaaa      300
tggaagatct cgacgacgat aagaagttaa agtgtagagg gtgcttgagg agcgctgga      360
aggattctgc ggaggggaccc atcgacgtag agacttgaag gcctactaag gtccacaaga      420

```

```

agccccggctc tttctccgaa tggtcggagc gtacagtatg cgacgtcgat cggcagacaa 480
gctggcggtgta gactcgaagt gttcgggcga atcgacttat aatagtcgcg cgctagtaac 540
gtaggaacac gaagagtagt cgaaagaaaa cgttttagtga gggaaaagat tagggaaaaa 600
ggagaggcctt aataactaag acacttggag cctaggccaa cgcgaa 646

```

<210> 629

<211> 617

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(617)

<223> n = A,T,C or G

<400> 629

```

gccccncccc cctcctnngg gcttatnngg acagaccac gtagtactct aaatcttctc 60
ctacgccgga caacggaccc tataccaatt cgaatcttgg aactccgac cgccggattc 120
tcttccccctt tcggcttccc ctttctgtcg gtacccctcc ctagtctct cctacacctt 180
cgtaccgtcg atatatagtc gccgcggact agcctattta ggtgtcctag actcgttatt 240
gatccactca ttagtctagt actatgcgtc acgtatctta gttgcctaag agggagatta 300
aatcctccac aagttccgac gaattcctgg actctcgtac tagcaaactt tcttatgagg 360
cttccttgta tatcttctgg atgtttctcg tgtcccggtc ctccgctact actagagctc 420
cttgccctat ctctagaagt agaggactct cgggttcggt ctccaaatct agcgctagag 480
ctatcgctac ccgctcgatt cccccagcgg aatcttgaaa cctgaggtag tacacaaacc 540
ctcncatct tccctcgggt gctccttctt ctcatcccc cttcccgctt tctcgggaan 600
gaatctactt tancttc 617

```

<210> 630

<211> 644

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(644)

<223> n = A,T,C or G

<400> 630

```

cnntcggcnt gggtttntt ctgagnnncc ccccccccc cccccccaaa cttacaccca 60
ccaaacactt tccgccccct acctaggaga cattagaagg gtttaggctt cggcgtatag 120
taaagtcctc tacctcggaa gtagagaatt cggtatTTaa attcagggtt agaggctcgc 180
tcgttagatt tatagtttag gtttagaata ggaaaccttc gatcttcctt agaagggtaa 240
taagttaggc cctaaatccg tctaaccaag gcgttaaggc ccgtacctaa acctagtctt 300
atcttctatc aggcgcacca atataggttag gttctacttt cgtataggcc ttaaggaata 360
gttcggtagt tatcgaaggc actcctctct aggctaggct tttctcagtc ttagtactcc 420
gggaccgtcg tcgcanaaat atcgatggac ggtagggtat tccgcgttac gcgtcgggct 480
agggatatag agcgaattat cggcgagagg cggtcgctan gaatcgggat caatatgntg 540
ttctttaccc tacggatata ggcagaaaac ataaaacctt ctnaccangg ataagggtatt 600
atcggacccc taaaataaca gtaacattta gantactagt accc 644

```


<222> (1)...(630)

<223> n = A,T,C or G

<400> 633

```
tccttcggct tgggtttttt tctgaccccc cccccccccc cccctcgga aggcctctag      60
gctcccaccc gtctctctaa tcctcaggaa ccgatccacc caaccaactt actaatgtcc      120
tacagtaaac acccgagaat ataaacccac acctaggcct ccaatcctac cagggaagca      180
agaagccgta gtctagcgta ttacgaaccc gagatagaga cggagatact tagttttatt      240
ctctcggaat aggaaagacg actggggagg gaatataggc tagcgcgggg ataggggcta      300
tggcggatat gggggcgggt cgctctctta ttcttctata ccacgtcaat aggaatgtag      360
atatacctag atgttcccgt agaaagagac gttagaggtc tccgaagcta taaaggagag      420
gcgcgaagaa acttcgtact ctagctttat ataggtagtc gctctagtcc cataagcgac      480
gagagatcta ctagatttcg gtatcgccgt cgtatgtatt cgaaatagtc ttcttccctt      540
tttcgatctc ctctctatac tacatggnga ttatagtctt aagatagtca ggatattagg      600
atattagtta tatgacgttc gacgggacgg                                     630
```

<210> 634

<211> 647

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(647)

<223> n = A,T,C or G

<400> 634

```
centcggtt ggggtttttt ctgaccccc cccccccccc cctccactaa gancttaacc      60
caaccctata gtttactcgt ataggggaat cgaggagaaa taggaacgaa gagcgggtga      120
taaagagaaa gtactttcct ttatatgtta agagcttagc gtaatgactt tcgttatatg      180
gctagttgat tttatccggc gttatagggc ttagttctgg ttatctcggg tctaattccc      240
ttagtatgct cgggagttta acgaggtcac gggatagcgc gtaccctttc taaggttcct      300
ggaaagctat tcgttattta tcgcgattct cgaggtcgaa aggatcaagg atcttccctt      360
ttactaccct agtcgggtta gcggtcggtc aaaactagtg tagtaccttt acctcctcga      420
aagttatagt cgaaacaacg tattagtcga aattatagcg gatagatcga gacggttcct      480
tctcgggttc tcagccggta atccctctat ttgggggtct tctccctctt cccctttgtc      540
ttccgcctta gcttccaagg ttccctcgga gcgaggggtt ctacttaagt cgntagcgtt      600
ccttataaac cncctacagg cagacccctt tgtaaacggc tcgggggt                                     647
```

<210> 635

<211> 645

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(645)

<223> n = A,T,C or G

<400> 635

```
ccttcgggtt ggggtttttt ctgagccccc cccccccccc cccgaaactc gccttaccct      60
```

```

agatacccaa agaatagttc cactcaactt cgtctaagta aaactctaga acttccaaac 120
ataaaagact tcgcgcggtt agctacacag cctacgggaa tctcacgaat cccgattcaa 180
gtcccactct cgaccacacc ccggtatcgt cgttttccca taccaatgtc gaaaaataaa 240
ataaaatcca gtcaagcccc acggtaaagc ggggtagggc taggcgaaga ggcaggaacc 300
gttcgaggcc gggggctttc aaaatacaaa acaactactt aaagtttacc ctttctaaag 360
tcgggggcaa cgggttaaagc acgcctctaa agtactactc gtttcgagaa ggggtagtca 420
tctcccgcat agagactctc gcgtatatca actcgcacgc cttctagcat tccgacggtc 480
gcccgcggtc acatatcttg cggattagct ccgagggact atagggttaa ttagtctagt 540
aaattctctt agaggatagt cggggtcgta gttaggcagt acgaggggac atggnctgcg 600
tcgtgctcta ccttgacagc atactcttat aaacatcttt ttctt 645

```

<210> 636

<211> 643

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(643)

<223> n = A,T,C or G

<400> 636

```

cttcggctt gggttttttt ctgaccccc ccccccccc cctagcggaa aacaatcccc 60
accgagattt tattaatcgt aaaactcgcc ttoggtacca agtcttctc cttcccgtaa 120
cctggctccc tcctagnngc ttacgaacg tccctctctt tcttacggct cggaagtggg 180
tacggttaaa tccgagngg gggctaacga atccaaggct aactcctctt anagtttggt 240
gtcncncgt ttagtaagga tccgtggagg gcgagtattt gnccccggc ctttattnta 300
tagttcccta gtacgataaa gntaccggct atcctattac agcggataaa agttatttan 360
agggccgacg tcnccgctag acaggctaca gctagnngag gtaccgcctc cgactantcc 420
gttgnttcg acaaggnagt ttcggttaac tccacaaact cctccgccga ctctanggtg 480
gggacggcag ttccncggtt tagtgtgctg tatagagaag ggcatttgag ttggacgtta 540
cnttttaaca taggttattc cgtttagggt cttgcgggcc cgtgggggta gtncccggc 600
gcgttnntat cggcgatttt ccgcagtttc cgtttccggn tnt 643

```

<210> 637

<211> 631

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(631)

<223> n = A,T,C or G

<400> 637

```

gggttntctc atttgggtgg actttttggg tcgtaggaac cggtatgnag gagtaggagt 60
cgctgggaag actagaagtt agctacggac gattagtgtg attccactct taataacgag 120
taatcgttta cgtcgggttg gtgtttcggg gttttggaga gtaagcgtag ttgtggagtt 180
tcgcatatag gtccccttac ttccggcagc tcgtcttctg tcggttaggt tattattggt 240
catccttcgc attagtagta ggggttggtc gataaatcga tagctattct ttagaattcg 300
tagtcggaga attcgtgtac gaagtccttt aagttcttta agttcgcgag taagacgtgt 360

```

```

acggttatatt tgtcgtcgac gtaggtgtcg ttacggggag tttcgtttta ggggttttacg 420
tagaacgtta ttaagcacgg taatacgata gaggattacg cgacgtattc gtcttagaac 480
gtcgattttt cgaaggcgca tttgttatcg aaggggagtc cttggagaat cgagatattc 540
caagaatatt acggagatta cagatcggaa ggctcccagag atcggacgta ttaccggtct 600
cgccccgaaac gagtaggtat cntccggata a 631

```

<210> 638

<211> 606

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(606)

<223> n = A,T,C or G

<400> 638

```

ccccccccc ctcaaccatc nattccccac ctcaacgcga attacggttt cgaaagtcga 60
caataagtcc ggtcgagtag aggggaatcag gggctgggtan aaaggaccac gggcggaana 120
taccggtctc cttccgggga ggcacgtcgg ggaaagggaa gagagcggtc tagttcgtag 180
gcaaacaggt cagaaaagtt aaggttaaag gtcggagggg agaggatagc tagtacgctt 240
agttcggggc tcgggcgcag ggccactttc ctcttttcgcg ttcctttact ctgcttacga 300
gttcaggctc cggagttccg cgccggaggt cgtcgcgacg ctaggaatgg ggactcgcgc 360
agtccccggt tacccttcgg gattctatgt tttcgcgcgag agacggagac cgggtagtag 420
ggttccgctc taccgccact cgtcgccttg atccggcccc ctccgcttaa gggcgatgaa 480
agattaggtt ttagggtctc acgggacgag gcatagggcg ggagaagggg ggaggggtcg 540
ggggtcgaag ggantaagaa atcgcantcg cgcgggggtcg gtagganccg aaatttttct 600
cnnctg 606

```

<210> 639

<211> 592

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(592)

<223> n = A,T,C or G

<400> 639

```

tcctcgggt tgggtttttt tctgagcccc ccccccccc cccccgggaa cgagaaaaca 60
atcccaccct accgcgggga gtgggttgna cgcttagttc tagaatcctc ggaatcgtcc 120
tcggcgcttg gtagttccgg cgattccgag tatgccgaag tgtatcgctc cgtctagagg 180
ttggtatctg tttatcgcca tgacgtatt gactcggatg ctttcgaagt agggggatag 240
gcgcatagat acgcctccgc ggtgtcctct gaagtggccg catccgtgga cgcagcgtag 300
acagctctgg tggacgataa cggtctctcg tactcctact ccggctatta tgtagagag 360
gacttgtttc tgaacggata taccattagc gaaggggtac cctccgctaa cgcaggcgtt 420
tctaacagtt cttccgggcg ctccgaattt agattgacgc ctccgcagca ttgtgggatc 480
ctcttcggtt agccctcttt ataggatttc tcctccgccc cgaaagangg ctggtcgtcc 540
ccggcangta tgtctagctc gaacgctttg ttactccttt gttttcgaaa na 592

```

<210> 640
 <211> 637
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(637)
 <223> n = A,T,C or G

<400> 640
 ctttgtggcg gtggntgtct catttgggtg gacttttttg gtcgtaggct tatccgggtn 60
 gggctcccgga agtagcttag gatcgccggc tagttccggt cccgcccgtc gaaagcgcg 120
 ttcggcgggc gggcccggt tcgttcggcg gctttaccct catagagtgc cagggtctcg 180
 ttcttacggg ttctgcggcg atagatttta cggcgagagg tcggtatctt cgccgcttta 240
 cgttcggtcg gcatctacgc ctagttcaca ggtagtttat gcgccggagc gcgtgacgga 300
 gaggttatac gggacgcgga agaaccgcct ccaaataact agtacaggct cgttcgggcg 360
 tagatctcct cgctcggtcg gcggttctta cttctagggc cgctctacgg ttaaggcg 420
 tcgttagatc tttagaaacta tactcaagtt tcagtcggaa gaaaggaagt agagagaagg 480
 gtaaacgatt acctccggtt ctagcccttt ttactcgcat aacgggagaa cggggtccgg 540
 ctctcagata cgcctcgcga gacgtcgcga ttcaacttta acctccgcta gggcatccgt 600
 atacggttaa cgcggtaaaa gcgacctcgg aaacctc 637

<210> 641
 <211> 649
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(649)
 <223> n = A,T,C or G

<400> 641
 ctntgtggcg gtggttgtct cagtttgggt ggatttttg gtcgtaggna acctgggatg 60
 aggtctagtt tcttcaacga ttcttggttc agttacgcga ccctatcctt atcttacaat 120
 gtcttctaca tcaggttcat caattaatat atcaattaca cattaacgac ggtgtgacgc 180
 aatatgagaa agtatacatt aagggtatta tatattatct gcttaaaaag gttcctgaca 240
 tgggacaact tcacccacca ttctagaagc cccccctcct gtaggacccc ctcgagttcc 300
 ccattatctt agttcagttt tcatttttta accaggaggg tatcggtttt taataggtac 360
 tattttgtca aacttttcag aagctttatc ttcaaataata cttgcacat ctgtactagg 420
 agcactaact attcgagtct attacagctc aacagaaaat aattgaaatt aaacaaccta 480
 agtatcgctc accataaccc catcgggctc tcaccccatc tcttcataag ttctagagca 540
 tcttgagctc ttctctatta ccttgatgg tactcatggt ctaatacccc ccgcagttat 600
 aggtccttat ggatcctatg ctaccaaccg tctaatacct tctatcacn 649

<210> 642
 <211> 645
 <212> DNA
 <213> Homo sapien


```
<210> 645
<211> 654
<212> DNA
<213> Homo sapien
```

[illegible]

```
<210> 646
<211> 645
<212> DNA
<213> Homo sapien
```

```
<220>
<221> misc_feature
<222> (1)...(645)
<223> n = A,T,C or G
```

<400> 646						
tccttcggct	tgggtttttt	tctgagcccc	ccccccccc	cccccaagcc	aagtacacag	60
accacacaaa	aacaacgtca	acacaacttc	gggtatacgg	accttaagag	agaccccgta	120
gtagacccta	ccacagccat	ccaatagtca	aacaacaagg	gcgcacccaa	tccatccata	180
gagctatcaa	acaacggagg	ggaaaggaaa	gagcagggtc	aacttagcag	agatcgaagt	240
cggcactaat	tcctttcaag	tactcgtctg	gcttgtagtt	cggggtaaa	tcgcctctca	300

```

aagggccaac gaggttttaa agcgaccccc gtatcgagtc ttcttcgtat tcattaaggc 360
gttaaaggta cgagacctag aagagagtag aattagccca ccaaatcgcc taaaccggca 420
aaaacgacca aaagtcaaag acccttaca atatacactt aaaacgcca ccccaaaaac 480
gcgatcagta acgcacgtac ctttccacg cttttctttc tttcactctc caaaacaaac 540
ccgaatatatt agcgcaaaaa atatacgagg gagaattaga agctattacc cgaaaaaaa 600
ncgganangg antaaatngt ggggaatana cgtttggttt ttctg 645

```

<210> 647

<211> 753

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(753)

<223> n = A,T,C or G

<400> 647

```

accttacctg gtaccgggcc cccctcgag ttttttttt tccaaataca actcagattg 60
tatacgaaaa gctgataata cattgacttt tgctgtttta atcccttgag ctttgataa 120
tgattttttt tgtgttaaca attgtagtat ataaaatcgg attcaccatc cttctgatgc 180
catattgatt agtttgattt tatggtgatg ggatcattgt gtgttaactg tattaagaag 240
aaatggattt gattgacttt gcatccattt ttatctgtgt tactttcatg ttttatataa 300
aagcatttct ggaccagaat aagttaagt gtataatttg ctttttacac gtttatataa 360
ttgaagttag caatgtggca aaatctctaa tggaaataaa atgcttcaga atgatgacat 420
aaatctgagc tatttcttgc ctggagaaca agtggttattc ataataattt aatagcttct 480
gaggtgtttt gttcatgtga tgaaggctta tccaccttgt atcaattcat gggctctgct 540
ttgtttaatg tagtcagggt gttaatacna gacttaagag tcacccact gtgataagt 600
gtgagtgaag attacatgtc ttangaaaat tatactggga atactcttga cattaatggg 660
tttaaagtgt ttaaggctag gggatgatgc aatgganaan atncttccaa angtttctgg 720
ttgtttatat ttgnngaagn catnaagana ccg 753

```

<210> 648

<211> 383

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(383)

<223> n = A,T,C or G

<400> 648

```

gatatcccg ggaaatgcgg aggcctttng gcttacgtgt ttaccgcgta gggcaaagcc 60
ttgncaaatt cccggccagc ggagcggcga ggggtggggac tcacgggaag ttaaacagcc 120
tcgtcggcgt cctcgaggct ccaaaaccag gctctaggcg gggacgactg cagccgttat 180
ggaggccacc gcggctacgg ccgcggctga ggccctccca ggtggagcgg tggcctggag 240
gggaatcttg atcctgggcc agccacctgt caagaggagg cggagcgtca tgcctctgga 300
agactggatg aatattctcc aggagcctga cgaaggcgaa gaagtctttg cagaggaaat 360
tgaatgctgt ctgatgctac aat 383

```

<210> 649
 <211> 349
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(349)
 <223> n = A,T,C or G

<400> 649
 cgattgtnta cnagtcttag agtaagctta agntcgntac cgagctcgga tccactagtc 60
 cagtgtggtg ggaattccat tgtgttgggt cactagtaaa tggatttagc tagacanagg 120
 anatttacc tttccattt agcacagtga gganaggcta nacagctagg atgcaataaa 180
 aaaaaatttta atgagaaatg tgtgtggttag attaatctta ttaatctcaa gttatagatt 240
 aaaaaatttta agtaccncat aaatgccatt tgcctttgct aangntacat ttttatgaan 300
 aangaccntg catacnaat ganatactgg actttnggna cttgangga 349

<210> 650
 <211> 306
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(306)
 <223> n = A,T,C or G

<400> 650
 cattgtgttg ggagcatcct tccatcagct cccatgagaa attctctgtt gggtttaagc 60
 aatccccaaa tatatcatat tgacatgaat atatcatctc ctcaatgtcc agcattagca 120
 gacaagatga gtgctgaaga tgatataact cctacctctt atgtaggcta gaggttaaagt 180
 ctggctctgc tgactgtggg gacataccga aaaggaatgt gggttaatat cagangacct 240
 ccctgcagat ccganantca gggncctggac tttctgggan aggaagcnaa aagttatntc 300
 tgaacc 306

<210> 651
 <211> 769
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(769)
 <223> n = A,T,C or G

<400> 651
 cattgtgttg ggcaggggtca tttctaaggc atgggctgga agcttttatt taaaacttta 60
 catgtcttag aagcactctg gttgttgcta ggcagacaat tttacatctc ttgctatacc 120
 agttgcatga agttcatcat gcatattggc tgtggaaaac cttaacagca tcatgtcata 180
 aggtttcagt aaggttttaa tgaaatcatg tattaagcac ttagtatagt gcaccttaaa 240

```
<210> 652
<211> 267
<212> DNA
<213> Homo sapien
```

```

<400> 652
nnangccctt taaccattgn ggctccacg cnttggggc cgtctacaa ctagnnggatc 60
cgcnactcta gnanaangat tggtcttnt gggntgggc ggcgggctg gggcggttaag 120
cggggctggg cgcgcgcgn ggttgnacna ggcgcgccg ccncacacn ccgggagcac 180
cctcnttgen gccntcccc gctaccccg cgcgcgcgn tccgcttttt ccncacccan 240
agcncntttt atctntgtct cctccgg

```

```
<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G
```

<210>	654
<211>	710
<212>	DNA

gctgntgaaa	gaccacaccg	aaaaactctn	ctttccgact	tccacatgat	gatnngcatg	60
tggtggtgag	agacttatca	tgacgacatc	gcttccnacc	atcgancncn	ctgcccaagc	120
ccattcatgg	aggcctgggn	anttctgtga	ntgacntnga	cncnanaenc	tnccactgtn	180

tgctatccag	acttgnttng	aatatnttat	tggcnaaana	canttncgga	atgctgtgnt	240
tgnn cattga	angatctgat	cactatgaga	gggtgaggac	nncctgctng	ctggcantnt	300
ntaaccn						308

<210> 657

<211> 696

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(696)

<223> n = A,T,C or G

<400> 657

accntttcca	caatnctgnn	ctccccgogg	tggcgggcgc	gtcgaccagc	aacctcagct	60
gtgggtcttg	ttacagtaat	gagttactgt	aaggaaagtg	tgacatttcg	agcaatttga	120
tttgtttaaa	aactagagca	gtttcagggg	tttccttgta	aatctgtctt	atgtgtcttc	180
aatgttcttt	cttgaggagt	agagaaagga	attgttagga	atgatgcata	aacctatggc	240
tattttatct	cgctgccacc	cataatcaga	gcagattctt	gggactatga	ccctcatgga	300
gacatgacaa	ttgtgtgtgt	gggtgggtgg	agaaaagagc	tggaattttt	tagggcttag	360
agggccaat	caggactatt	ttatggagct	ctgctcacca	actttaagtg	agcaccaggg	420
gtgngaaaag	gaatcttggt	ntcaaaaana	caatggnaag	gggtaagttg	gtatnctgaa	480
ctggccactt	cggactctta	tttaactggg	tattctcant	taaggaggcn	nggggtggtc	540
tggcttgtna	aggaaaagcct	gtgcaatgga	atgactttta	aaccccccat	taaaaaaaaa	600
angntataaa	tcttggtgtc	taanaangaa	gcctgggttc	tnttanccca	ttttnccccc	660
gggaaggnaa	atnttcttag	gnaanggaag	ggaagg			696

<210> 658

<211> 698

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(698)

<223> n = A,T,C or G

<400> 658

ctggactccc	cgcggtggcg	gccgtctctag	aactagtgga	tccgtgttgg	ctcaattctc	60
aaggtctgtg	ctgtgcggcc	tgttccccac	acgtgctgct	cagctcaggc	aagcaccgag	120
cttgtgttgt	ttcatgctca	gcgtggaggc	ccctcctcca	ggtcgctgct	ctgtgggggt	180
cccatacact	caggctccta	ggaggagtcc	atttagaaag	ccagggtttt	tctcagagtc	240
ttagttcctt	gtgctgtcat	ccatttcaca	cgacttgggc	cctgctcggg	gcaacacagc	300
aagagaaaag	acagggaaaa	taagagaggg	accttgacac	cacacgctct	ggaccacaga	360
gccctgtgcc	cagctcctct	gtcaatacac	gtggaatctc	gtgcaggatc	gcaggggtct	420
gtgatgccac	caaagagcag	gccgggacag	ggttaggaga	gaaaggagag	ggaagtgggg	480
gtttctccta	cgcactctta	tttgagaggg	gaaaggcggg	tttgtattgg	ggttgctcgt	540
ctttgcaccc	acngcacagt	tgtgagacac	ccccatcctn	agatcaaagc	cccacataca	600
gcttggggaa	aaacaaaacn	aaacaaaaca	aaaacagtaa	acctccatgc	canttggttgg	660
gnaagttttn	aatttinctc	cccnacccan	cttgccttc			698

```
<220>  
<221> misc_feature  
<222> (1) ... (750)  
<223> n = A, T, C or G
```

```
<210> 660
<211> 849
<212> DNA
<213> Homo sapien
```

```
<220>
<221> misc_feature
<222> (1)...(849)
<223> n = A,T,C or G
```

[illegible]

849

<211> 653

<212> DNA

<213> Homo sapien

 $\langle 220 \rangle$

<221> misc feature

 $\langle 222 \rangle \quad (1) \dots (653)$

<223> n = A, T, C or G

<400> 661

aacttaagct	tggtaccgag	ctcggatccc	tagtccagtg	tggtggaatt	cgcggccgcg	60
tcgacctcca	ttcgttttctt	gtcctttttt	ttcatttttt	ctcatgttct	attcacttta	120
ggtttctaag	ataaatatta	taaaataatt	tttacttata	aattattcac	tgataccctg	180
tctttaacat	gtgaaatgaa	ttcaaaagga	atcttaatga	gaaataatat	actcatgatg	240
tttaatagat	ttgatttcga	aataataagc	cctctgaagt	cctaagttaa	aaataaagca	300
acttgtttga	taatttttca	tcaagaatgt	atctgagtct	ctgagtaatt	attagtagga	360
atattccatt	atcacaatta	cacagtataa	gctatttagt	ctaactttac	caaaaaaggg	420
agctacttca	acactgtgtg	agacttttta	tgggtttgca	ttgggtatgc	actattagca	480
agataaccta	ttttacagca	gtggttntta	acctttccca	tttatttgaa	aggcgactaa	540
gatatagctag	ttaatntaan	gggctgatgc	atttatatta	catgtagana	atggggagata	600
cnaaaaggaq	nqaaaggaana	ntttttgnat	tcnnaagcct	cnttgncaat	taa	653

<210> 662

<211> 646

<212> DNA

<213> Homo sapien

<220>

<221> misc feature

$$\langle 222 \rangle \quad (1) \dots (646)$$

<223> n = A, T, C or G

<400> 662

aaacttaagc	ttggtaccgc	agctcggatc	cctagtcacg	tgtggtggaa	ttcgcgccgc	60
cgtcgaccca	gggacaggca	gccagnctg	gggtcaccag	ggtccctct	tgggccctcc	120
aanagcaaca	gtactggcaa	cagctgggat	ttgctgagca	cagactctgc	agcaggctcg	180
gttgagctct	ctgtgcctgt	tccttcatac	catcctcacg	ccatccatg	agatgggtcc	240
agctgttttc	agatgagaaa	atggcacagg	aagctggtaa	gtgacagtca	gaaatgaatg	300
ctggcagctt	antccttggg	cccaccgcag	tgcaggacct	tgtcaacag	ggatcacccct	360
tgtccgccac	ctgttcattg	ggccacccag	ggtttgtgtg	gtcatttgtc	tcctttccatc	420
tgcttgcttc	caaccagctg	ggctcattag	gctggggaac	ccagacccca	cacagtccct	480
ctcccgagang	ccagacacac	nctnccgcac	agnaaggact	tcagtccccg	aancaaattgt	540
ncctgggcgt	anaaactgna	gggnccccaa	tccttggtgg	ggtactgctt	tgcactggng	600
gaattcaccc	ctcattgnna	acctttccct	nttnnccacc	ctaaac		646

<210> 663

<211> 650

<212> DNA

<220>

 $\langle 222 \rangle \quad (1) \dots (650)$

<400> 663

<210> 664

<211> 678

<212> DNA

<213> Homo sapien

 $\langle 220 \rangle$

<221> misc feature

 $\langle 222 \rangle \quad (1) \dots (678)$

<223> n = A, T, C or G

<400> 664

<210> 665

<211> 694

<212> DNA

<213> Homo sapien

<220>

<221> misc feature

<222> (1)...(694)

<223> n = A,T,C or G

<400> 665

cttttcaaat	cattttttnct	cttctaggta	tancctgtca	ggtggcctaa	tgtaatTTTT	60
gacatctcta	ngaattttta	tagaaccaga	aatgggtgcc	agagatatgc	ctgcactaat	120
cttaagtggg	gatttatgta	tttctcaagc	aagtgattaa	agcaaaacta	ggcacgattg	180
aaatcaagat	cttttaggca	anaaagtcac	gatgagtttt	agaattattt	taggactctg	240
tggctttctc	ttcatagaaa	tagaaaaaaa	aattgtataa	aaccacaaaa	ggtcctgaat	300
agccaaagca	acactganca	aaaagaacan	agcagggaag	caacacacta	ccngaattca	360
aattatacta	ccagggtgta	gtaacccaaa	cagcattcta	ttggcataaa	atagacacca	420
agaccaatgg	ancagaataa	agaacccccac	aaataaatcc	atataatntac	cgccanctga	480
ttatcaataa	cnaacaccaa	gaacatatnt	taagggaacnt	ncatttcaat	aantagtgtc	540
ggnaaaaaact	gggaaatcca	tatgcagaaa	naatgaaact	agacccctat	ccctcaccat	600
acgcaaannt	caacttcgga	atgggattac	aaaacttaag	acattccaac	ccaagaaact	660
atnaaancta	ctattaagaa	aacagatcnc	nccc			694

<210> 666

<211> 705

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(705)

<223> n = A,T,C or G

<400> 666

tttaaaaatt	tagatacact	angaaaatta	tttttagtata	agaagaatat	caggggggtgt	60
agtactcatc	agagctaaat	gagagcgctt	taaaaatggt	agtttgtctt	ccgccatttc	120
tacagaaaagc	tgcaatttca	ggtttttcaac	ctaatagggtg	atattttaaga	aaaaaaaaaa	180
gcaatcgcaa	atagccccac	tgctttttaca	aatcattttt	tctcttctag	gtatagcctg	240
tcagggtggc	taatgttaatt	tttgacatct	ctaggaattt	taatagaacc	agaaatgggt	300
gccagagata	tgcttgcaat	aatcttaagt	ggggattttat	gtattttctca	agcaagtgtg	360
taaagcaaaa	ctaggcacga	ttgaaatcaa	gatctttttag	gcaagaaagt	catgatgagt	420
tttanaatta	tttttaggact	ctgtggcttt	ctcttcatag	aaatagaaaa	aaaaattgta	480
taaaaccaca	aaagggtcctg	aatagcccaa	gcaacactga	acaaaaagaa	caaagcagga	540
agcaacacac	taccagaatt	caaattatac	taccaagggtg	tagtaaccaa	aacagcattc	600
tattgggcnt	aaaatagacc	naagaccaat	ggaacagaat	aaagaaccca	aaataaatcc	660
atattttttac	agccagctna	ttatcaataa	aaacnccaag	aacnt		705

<210> 667

<211> 817

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(817)

<223> n = A,T,C or G

```

<400> 667
nnangacttt tgtggnttta tacaattntt ttttctattt ctatgaagag aaagccacag      60
agtcctaaaa taattctaaa actcatcatg actttcttgc ctaaaagatc ttgatttcaa      120
tcgtgcctag ttttgcttta atcacttgct tgagaaatac ataaatcccc acttaagatt      180
agtgcaggca tatctctggc acccatttct ggttctatta aaattcctag agatgtcaaa      240
aattacatta ggccacctga caggctatac ctagaagaga aaaaatgatt tgtaaaagca      300
gtggggctat ttgcgattgc tttttttttt tcttaaatac cacctattag gttgaaaacc      360
tgaaattgca gctttctgta gaaatggcgg aagacaaact aacattttta aagcgctctc      420
atthagctct gatgagtact acaccctga tattcttctg atactaaaat aattttccta      480
gtgtagtcta aactttttta aaaagacatg taatccgagg agtttgtaac tcaaaacgag      540
tgcacttagg aggtatcgca agccgtttct ggattaaatt ccagctagc ttgcttgctt      600
agcaggggag gnaaanaag acatctgcag cctagggag aaacaccttc gcattgttct      660
tacgtgttta cgttatttta tttcctanaa caaggcngaa ttgggactcg aatggttcag      720
ttgggggtggg ggatcccctg gtncataaaa ngtcanaaag anggtacagg cggaacncca      780
agggtcgtcc tgcatttana ctcggaatth ttggtgcc                               817

```

<210> 668

<211> 826

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(826)

<223> n = A,T,C or G

```

<400> 668
cgggggggnnt tacgtctctc tggacgcttt tattgtacca gggcgatccc agcccaactg      60
taccattcga gtcctactc ctgccttgct ctagggaat aaaataacgt aaacacgtaa      120
gaacaatgag aaagcgtttt cttccctagg ctgcagattg tcttcttcac cgcccctgct      180
tagctagcta gctagctggg aatttaaatcc agaaacggct tgcgatacct cctagatgca      240
ctcgttttga gttacaaact ccgcggatta catgtctttt taaaaaagtt tagactacac      300
tagggaaaat tatttttagta tcagaagaat atcagggggg gtagtactca tcagagctna      360
atgagagcgc tttaaaaatg ttagtttgct ttccgccatt tctacagaaa gctgcaatth      420
caggttttca ncctaataag tgatatntaa gaaaaaaaaa acaatcgcan atagcccact      480
gcttttacaa atcatttttc tcttctaggt atagcctgct aggtggccta atgtatthtt      540
gacatctcta ggaattttta tagaccagaa atgggtgcca gagatatgcc tgcactaatc      600
ttaagtgggg atttatgtat ttctcaanca agtgattaaa gcaaaactag gcacgaatga      660
aatcaagatc tttaggccag aaatcatgaa nanttttana attattttan gaatctgtgg      720
cttctcttct taaaatngaa aaaaaaattg tttaaaccca naaggctctga atacccaagc      780
nccctgaacn anagaacaan gccggagcac cccctcccaa atcccc                               826

```

<210> 669

<211> 547

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(547)

<223> n = A,T,C or G

```

<400> 669
cattgtgttg gggaaaaaat gatttgtata agcagtgggg ctatttgcca ttgctttttt      60
tttttcttaa atatcaccta ttaggttgaa aacctgaaat tgcagctttc tgtagaaatg      120
gcggaagaca aactaacatt tttaaagcgc tctcatttag ctctgatgag tactacaccc      180
ctnatattct tctgatacta aaataatttt cctagtgtag tctaaacttt tttaaaaaga      240
catgtaatcc gcggagttag taactcaaaa cgagtgcac tnggaagtat cgcagccgtt      300
nctggatnaa attcccagct tgctngcttg ctncgcccgg gggcggtnaa aaaaacatct      360
gcagcccnng ggnaaaaacc ttgcatttgt tcttacgtgt ttacgttatt ttatttcctt      420
nnagcaaggc nggganttg ggactcgaaa tggtagcgtt gggctgggga tcgcccttgt      480
tacataaaag ncgtccagaa gagggacggt tacaggcnng ganctccaaa ggtcagtcct      540
tgccatt                                         547

```

<210> 670

<211> 232

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(232)

<223> n = A,T,C or G

<400> 670

```

cgaactatct agactaccta ggaaaattat tttagtatca gaagaatatc aggggtgtag      60
tactcatcag agctaaatga gagcgcttta aaaatgttag tttgtcttcc gccatttcta      120
cagaaagctg caatttcagg ttttcaacct aataggtgat atttaanaaa aaaaaaagc      180
aatcgcaaat agccccactg cttttacaaa tcattttttc cccaacacaa tg              232

```

<210> 671

<211> 214

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(214)

<223> n = A,T,C or G

<400> 671

```

ctccccctcc ntccctcget actnncnatt ttcnnaaatt tntttcgcnt atngggaaaa      60
acaccacat tnttcanctc gcacagaaca ngngggggtg tgtaaaatga agggcttccn      120
cnctttctct tattnaanaa cactnaaana gggangggct aaaacccgcg ngatntctac      180
nctatcgcg gcgcttttgg ngttggctag aaga                                         214

```

<210> 672

<211> 328

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature
 <222> (1)...(328)
 <223> n = A,T,C or G

<400> 672
 ngancagcgg ngtttaaacy ggcctctaga ctcgaggaga cncctgttgg atggtggatc 60
 acanntcgt actactatac aggacagagt atcggganct cttggntggt ggngcctgcc 120
 aaccactgct nctgttaact gcgtatctga agggactcgg actggcttca gaagaactac 180
 cggctcgaat gnaccatgga tgattcncnc tagttgaaaa aaaactcagg cacatgtatt 240
 gccactgatg actagcgcca gactnctctc ggctctntaa cgagcccaca tgncngtgtg 300
 ncncctgtgc tgnctccaga agagggttc 328

<210> 673
 <211> 223
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(223)
 <223> n = A,T,C or G

<400> 673
 gggggcaaaag ctggctagcg tttaaactta agcttggtac cgagctcggg tcccnagac 60
 attgtgcatg aaaatgcaaa ttgagtgtgg tctatantgc catctcacc tctgncngc 120
 tcaaaacaac ngctttctgc tgcaatgggt agggctcctn acncacggtc gcnnacggag 180
 gccncttat cctctcgggt nnggatccct ngaagcatnt tct 223

<210> 674
 <211> 256
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(256)
 <223> n = A,T,C or G

<400> 674
 gnggggtent ngatgagcgc gcgtaatacn atcactntcn ggcgngntgg gtaccgggcc 60
 cccctcnaa gcggccgcc ttttttntt ttttttcatt acatgataa ntctttnttc 120
 taaacagacc acaccactan agttcctttt ctttngtacg gaattgagtt aaagtagagn 180
 atacaatgca gggcttcnnc tctatttcac attccaggnt ggttcngnat ggatcggccc 240
 tgctctccg atgggt 256

<210> 675
 <211> 439
 <212> DNA
 <213> Homo sapien

<220>

<221> misc_feature
 <222> (1)...(439)
 <223> n = A,T,C or G

<400> 675
 nnactagtcc agtgtggtgg aattccattg tgttgggctt gtatggggtt ttttgtctag 60
 ttntttggga aatgttngtg ttactatntt ttggatatna tatatgatat gtatggccct 120
 tctatgggct cctcanacng aactcaacca ttttccacaa aaccnattcc tcctttccct 180
 tcatgactga gtggtgttgg tactatccng gaaactggga cattgtcctt cacatctntc 240
 ccttanactgc ctngtccnat tgatgtcttt gagctntgan atgtctttgt taactntctc 300
 ctntntctgt actgccggca naattaagca ccatntgtca caaaaagtat tgcgttacct 360
 tcacgnatct gttngttncc atncttgctg cttctccngn ggaaaatagg ctnttctggc 420
 aaccgaacng aanaaatac 439

<210> 676
 <211> 587
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(587)
 <223> n = A,T,C or G

<400> 676
 ngngggcctn attaagcgcg cgtaatacna ctcactntgg ggcgaattgg gtaccgggnc 60
 cccctcaagt tnatntgccn aacctctctt ttggaataac aaaagggttta acacatatgt 120
 cctcataggg acgcgctttc acacnttccg gacngcttca tanacntcat tntatattct 180
 cctcagnaca agttnaggcn gaagggtgagg canacnttat aatttccatt tcacaaatnc 240
 ggaaagttag gctcaaaggg nttaaaaaat aacctgatac aantcataga gccggtntct 300
 ggaanaagca ggagcaaagt ccaggcatcc tgatccaagc tnggtccact gccttccact 360
 ctggagaggg ttcattctccg acaaaggaag ggacntgagt ggctgganaa tctcatggga 420
 taaagacctc agnatttcat gctcctggaa atcccatggg ttgaacaaca ggtntttggc 480
 ccgtggttct ntccctttgn ccatctttta accttggggg aaatgatggc ntctntnagc 540
 nttttttttn aaagagatng aaattgaatg attattngct cattggg 587

<210> 677
 <211> 444
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(444)
 <223> n = A,T,C or G

<400> 677
 gtggggcatn attaagcgcg cgtaatacga ctcactatag gggcgaantg ggtaccgggc 60
 cccctcgaa gcggccgccc tttttttttt tttttactgt ccaaactntc tatngatnta 120
 gttgaactgt ncaacgattt catgaaatcc tatacacana gccttcaggc ccagagagta 180
 aaacaaatth aaatttnttc accanattgn agcagncana agcatccnat natatccgac 240

tacaatgaat	natatgctna	nggtanctna	tttaccact	ntgggggtctt	tanggtctgt	300
cacaaactat	tttcgtaaac	atcnntttaa	anttnnggtga	atggacctaa	tnccagataa	360
ntctatttna	tnaccctag	catncctgtg	gctnactttt	cgggctgtgt	tggcntactt	420
ttaggagaaa	attggtataa	atnn				444

<210> 678

<211> 670

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(670)

<223> n = A,T,C or G

<400> 678

actagtccag	tgtggtggaa	ttccattgtg	ttgggagcag	tttaaaaaaa	aaaaagacna	60
aatatacnac	tcttgatnaa	acataaaggt	acagtgggtct	atgaggaana	gaaaaggtac	120
ctnaggatgc	aaaantacct	accacatggg	aaccgttngt	ccacactcat	tcnnanaaaa	180
accgagtcct	ctcanttnca	cacgtgtacg	tttcagttgg	gaagtgcttg	ccattactcc	240
naagcctaga	accttcacgt	cctgaagggt	ctggaagggt	tttcagattg	cttaaganac	300
gcngcccttc	catattcntc	tcactaccc	nggggaacgg	aacaaatgga	gctgcgacng	360
ggaagcgtcc	cttcccntcc	gaacgctttc	tttcaaacct	gcctgccttc	cnggcgaatg	420
gaccggaagg	tttncnngct	tcctttcanc	ccnaattact	tcctgngttg	aaaattggcc	480
tgttggtttg	caaatgcngg	aatttgttta	ctttcntcat	gtcctgtgtt	gnncnaaccg	540
gctcncctgt	tgccctccct	tngaaagggt	ttcatcaggc	cccgcctttt	ctcttntaan	600
ngtcctaate	cggncnggac	cactcgggga	aaattttttc	ttttcgaaaa	gccgccccnt	660
ccgtccggct						670

<210> 679

<211> 449

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(449)

<223> n = A,T,C or G

<400> 679

actagtccag	tgtggtggaa	ttccattgtg	ttgggagtag	gtctactaca	ncctacttcc	60
cctatcatan	aaganccttan	caacnttcat	gatccccccc	tcntannoct	tttcctcanc	120
tgctccttag	tcctgtttgt	cctnttcccta	acantcntaa	ganagatnac	taatnctact	180
atctctnacc	tcgggaanct	acaanacgtc	tggaactatt	cngaccccat	gcancncat	240
ntcccatcgt	cctcccagcc	cctncccttc	ctttacntta	ctnaacgaag	gtcgacgatc	300
cctcccntac	ctcccnnncc	attgggnccc	aanggnactg	gacctcacga	ntacaccnac	360
tacgggnga	ctaagnctgn	aactccttac	atatntcccc	gttacccecn	gaacncagcg	420
aacngcnaca	ccttggaant	caagaanta				449

<210> 680

<211> 670

<223> n = A,T,C or G

<400> 682

tgatcattca	agcgntgngc	gnataacgat	tgctnagccc	aacctttcat	agggtcgttc	60
ctttgggaat	nggatgtcta	ttgaatggca	gggatagggg	cactcggcac	tcgcctctgg	120
tacagttttg	catatatatc	ctcatcgcca	gcgagcgtag	gggancgtta	agtttgggga	180
aatgccnccg	catgncctn	ccggagctta	aacccccaac	aatnccatt	ttnaaaaaag	240
ntttnttant	taaaaaaaaa	aac				263

<210> 683

<211> 255

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(255)

<223> n = A,T,C or G

<400> 683

cttgcccggc	atgcacagac	ntntttacgg	acacnctact	ccaagngagc	ctgnanctgt	60
ctacgggtcaa	nctctaaggt	tnngncantgc	cacanatggc	atagtcccga	gggcggtnan	120
tctggantgc	tctctgcact	tgaacntaaa	gcgcntttca	aganaggnc	aatngcctgc	180
ctcttgacaa	cnaacaancc	cacaccnacc	tangaccctn	tangcaagga	ctggattctg	240
naaatgcaat	acaca					255

<210> 684

<211> 922

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(922)

<223> n = A,T,C or G

<400> 684

acctttcatt	tcattgtgctt	ctatttttcct	acatcttttta	catgactaag	ggattaatga	60
aatcacctct	tcataatcat	gaccataaatt	tcataccaaca	agtactcaag	tttggtgtta	120
gcacttttatt	aatgcttacg	aattctctct	ctctccctct	ttctcttttc	cttagtcctt	180
gcacaataag	gattttttgaa	tgtataatat	catcttaggt	aagctttcat	atggtttttg	240
catatgaagc	ttatgactgt	cataagccat	accaagcctg	tggagtatgg	catgattttc	300
attacataat	ccaatgaaaa	tagacttatt	ttaaatccct	aactttgtag	ttttaatttg	360
tatttcacta	tcttgaaatt	aacagctagt	acttatccat	cacagcagtc	tcctactgac	420
atgaagcaag	ttgttgaaatg	cagtagancca	tgaatgaaag	catttaaatgt	tanacaaaaa	480
tgggtgatac	ccaagcattc	tgaattat	gcatacaagga	atgggacatg	tacattagtg	540
gcatactttc	taccaatatg	tgacttgaat	tgtttttttta	aaaaaaggan	aatgantttc	600
tcaatttgct	ttaaaaaatt	ttnaaaaagt	tcaatggcat	gctgctttgt	ctggacttaa	660
tttattaaca	attnttaanc	cttccttaag	gacanaat	tggtgttcag	gatcnccttg	720
aagggtctta	tttttnatan	nattccaaac	ccaaaagggtg	gtttaaaatg	ggnggggttc	780
ccccncnaaa	atttggaccg	gcttttttat	atttaaaaaa	nttnccnttt	gngtttgaaa	840

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nctnaatacc aattaagggg gaattttacc tnccagtggg aaaaaaaaaac nctngccntt 900
naaaaaattc ccnggagnca at 922
```

<210> 685

<211> 531

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(531)

<223> n = A,T,C or G

<400> 685

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tctttaattg gcatggaaga ttcattgttc caaatctcag atgaagatcc tatattggat 120
gcaattaagc ctggcagcgc cctcaaaaga cagtcttgtc actgctagcc acagccagga 180
cacagtaaca gttccttcta gtgacccnag accataanaa atananatct aaagaattct 240
gactccaaag gcattagccc attcctggta ttgccaatga tgatagaaaa aattgccaaag 300
ctcctgggac atggaaatac actcagtaca tttgagaact ggagaactan tttccaaaat 360
agtatgaaga catganggtg attgtagata tntgagtttg gagaanttga gggaaatcng 420
attacacatg tttactacaa gagatgttna taagtaaaga aggcctgata tacaatctaa 480
cagacnantg agataaatct taantcacia ctgaentccc ttttggggcg g 531
```

<210> 686

<211> 336

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(336)

<223> n = A,T,C or G

<400> 686

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ggngncctna tgagcgcgcg taatacgatc atatagggcg aattgggtac cgggcccccc 60
tcaagaacac tacaagctat gtcctcttct canagagccc tgaantttta acatattgaa 120
agctctnatc ttgccaanaa actccactta acttcaaaac acaccctcca cacacatcat 180
gatcaactna gatcttactg aaccagaatc ctnaatggca tacttcagga acaggggtcc 240
anagaagcag ttctcaaant gcagctnaaa aagaaactga aaaccaatt catgcaanac 300
ctagggctta tttgagagca ttttcagtg cagatt 336
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<210> 687

<211> 271

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(271)

<223> n = A,T,C or G

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<400> 687
aatctgcact ggaaaatgct ctaaaataag ccctaggtct tgcatagaatt gggttttcag      60
tttcttttta agctgcactt tgagaactgc ttctctggac ccctgttcct gaagtatgcc      120
atntagatt ctggttcagt aagatctcag ttaatcatga tgtgtgtgga ggggtgtgttt      180
tgaagttnag tggagttctt tggcaagatc agagctttca atatgttnaa acttcagggc      240
tctctgagaa gaggacatag cttgtagtgt t                                     271

```

<210> 688

<211> 740

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(740)

<223> n = A,T,C or G

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<400> 688
tgatgaagcg cgcgtnttac nactcactat nggggcgaan tatgggtacc gggnccccct      60
cgaagcggcc gccctttttt tntttttttg tgagagttta aataaaatat ttgagtttaa      120
tttaaagttt gagtttaatt aaaatatatg gcatatccca agttgggctt tgcanaaaga      180
acacttctca ggaactgtta gttggtgtac caggaactca gaagggtcct gttattaaat      240
atatttgtaa aatgcatgga ttctctgaan atcnctctgc atgtgagcaa cacttacatc      300
ncaaaccaaa attggcattg catacatnaa ccaatatttc ccaaacattt ctgggttatgg      360
cccacccctt ttgtgtanta cttattgctg ttttttgtaa ccctggggaa attacttaaa      420
atattcagct ggaaattaca ggcgttactt ttaaggganc aagaattaca gtgactccca      480
aaattgcaag tgttgattac tatttaagaa cccaagaatt tgaaagaaat tttgaaaagt      540
gaaaacngga aatnttaaat gacttctcaa attttgaaaa ctcnngnaaa catctccact      600
ttggtncctt tccttttaaaa attggctaaa aattntttnt tatnccacc ccattggaan      660
tncccccccc ctggaacaat tggattcccc tatttcctaa aaaacggccn cccccccg      720
ggngaacncc nacnttttgn                                     740

```

<210> 689

<211> 635

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(635)

<223> n = A,T,C or G

```

<400> 689
actagtccag tgtgggtggaa ttccattgtg ttgggattac atatactttt agcaattttt      60
aaagaagtgt acaaagttga gatgtttcct gagctctcat atatctgana atgtcatttt      120
acatctccgt cttcacctct caaaacttct ttcaattctt tggctcttaa tagtaataca      180
cacttgcact ctggagtcac tgtaattctt gctcctttac agctacncct gttatttcca      240
gctgaatatt tttagttatt tcccaggggt ccaaaaaaca gcaataagta ctacacaaag      300
gggggtgggcc ataaccagaa atgtttggga aatactggct catgtatgca atgccaaatc      360
tggtttgcna ttgtantgtt gctcacatgc agagtgaatc ttcaaanaat ccatgcattt      420

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tccaaatata	tttaataaca	gggaaccttc	tganttcctg	gntacaccaa	ctaacagttc	480
ctgaaaaatg	ttctttctgc	aaaacccaac	ttggggatat	gccatatatt	ttaattaaac	540
tcaaaacttta	aattaaactn	caattatttt	atttttaaact	cctcaaaaaa	aaaaaaaaaa	600
agggggggcc	cttccaangg	gggggnccggt	tcccc			635

<210> 690

<211> 3923

<212> DNA

<213> Homo sapien

<400> 690

acagaagaaa	tagcaagtgc	cgagaagctg	gcatcagaaa	aacagagggg	agattttgtgt	60
ggctgcagcc	gagggagacc	aggaagatct	gcatgggtggg	aaggacctga	tgatacagag	120
gaattacaac	acataacttt	agtgtttcaa	tgaacaccaa	gataaataag	tgaagagcta	180
gtccgctgtg	agtctcctca	gtgacacagg	gctggatcac	catcgacggc	actttctgag	240
tactcagtgc	agcaaagaaa	gactacagac	atctcaatgg	caggggtgag	aaataagaaa	300
ggctgctgac	tttaccatct	gaggccacac	atctgctgaa	atggagataa	ttaacatcac	360
tagaaacagc	aagatgacaa	tataatgtct	aagtagtgac	atgtttttgc	acatttccag	420
cccctttaaa	tatccacaca	cacaggaagc	acaaaaggaa	gcacagagat	ccctgggaga	480
aatgcccgcc	cgccatcttg	ggtcacgat	gagcctcgcc	ctgtgcctgg	tcccgcttgt	540
gagggagga	cattagaaaa	tgaattgatg	tgttccttaa	aggatgggca	ggaaaacaga	600
tcctgttgtg	gatatttatt	tgaacgggat	tacagatttg	aaatgaagtc	acaaagttag	660
cattaccaat	gagaggaaaa	cagacgagaa	aatcttgatg	gcttcacaag	acatgcaaca	720
aacaaaatgg	aatactgtga	tgacatgagg	cagccaagct	ggggaggaga	taaccacggg	780
gcagagggtc	aggattctgg	ccctgctgcc	taaactgtgc	gttcataacc	aaatcatttc	840
atatttctaa	ccctcaaaac	aaagctgttg	taatatctga	tctctacggg	tccttctggg	900
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ctgtgacctt	tctacactgt	agaataacat	tactcatttt	gttcaaagac	ccttcgtgtt	1020
gctgccta	atgtagctga	ctgtttttcc	taaggagtgt	tctggcccag	gggatctgtg	1080
aacaggctgg	gaagcatctc	aagatctttc	caggggtata	cttactagca	cacagcatga	1140
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tagtatctta	tataatatac	ttcatttctc	tatctctatc	acaatatcca	acaagctttt	1860
cacagaattc	atgcagtgca	aatccccaaa	ggtaaccttt	atccatttca	tgggtgagtgc	1920
gctttagaat	tttggcaaat	catactggtc	acttatctca	actttgagat	gtgtttgtcc	1980
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ttaaaacaag	catgttttca	aatggcacta	tgagctgcca	atgatgtatc	accaccatat	2220
ctcattattc	tccagtaaat	gtgataataa	tgtcatctgt	taacataaaa	aaagtttgac	2280
ttcacaaaag	cagctggaaa	tggacaacca	caatatgcat	aaatctaact	cctaccatca	2340
gctacacact	gcttgacata	tattgttaga	agcacctcgc	atttgtgggt	tctcttaagc	2400

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aaaataacttg cattaggtct cagctggggc tgtgcatcag gcggtttgag aaatattcaa 2460
ttctcagcag aagccagaat ttgaattccc tcatctttta ggaatcattt accaggtttg 2520
gagaggattc agacagctca ggtgctttca ctaatgtctc tgaacttctg tccctctttg 2580
tgttcattga tagtccaata aataatgtta tctttgaact gatgctcata ggagagaata 2640
taagaactct gagtgatata aacattaggg attcaaagaa atattagatt taagctcaca 2700
ctgggtcaaaa ggaaccaaga tacaaagaac tctgagctgt catcgteccc atctctgtga 2760
gccacaacca acagcaggac ccaacgcatg tctgagatcc ttaaatcaag gaaaccagtg 2820
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ttccaataga tgctgcctat gggctatatt gcttttagatg aacattagat atttaaagct 3120
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tacctaattg atgtgggact taaaacctag atgatgggtt gatagggtgca gcaaacct 3840
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<210> 691

<211> 882

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1) ... (882)

<223> n = A,T,C or G

<400> 691

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cctgcactcc agcctggatg acagaacacg atcattttctc taaagacaaa caaaaaacat 120
aaaataaaac tagtataagg atagaagccc agggttgatt taagtctgcg gaaatcataa 180
accataggtc agacttctca ttgatgaggt acttggtgggt tagaatacaa ttaggtatat 240
ttggtctaga aaccaggatg gaattagaga ataaaagact gagcaatagc atgttatagt 300
attagaaata ctatagaaat aggaaaagcc ctgattatga ctttggagtt ctgatccaac 360
atctgggatt atttagatat tttaaaggaa aacgatgact ttttagctctc aggatgttag 420
tttctcctca cataaaatga agagcctcga aaagatttctg tttaccagat tatttctgaa 480
gtcaattcca gttctaaaat tccatcactg ngcactaagg caaattgaat tgaataaaagt 540
attgggnatg cataaaatag tctattttta aaaangaata gtaattatcc attggnaaca 600
gacgcantca tccagncatc tcctaccctg ncccatgnen tatgtagana tgtanctcta 660
atcccttaac aaaccgattt tgcaaaggag cttanccttg gggtaacttg tcanggcaac 720
tgggtctact tnaagactca tcttcaacta ctgggcacca aatncctacc attgcatcaa 780

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actgggggttc ccatncaagg caaacccctgn gaaatcttta atccccgaaat tggcgcccaa 840
 ttttgngggg tttccnaaaa gaatcntccc ccccgagggg cc 882

<210> 692

<211> 235

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(235)

<223> n = A,T,C or G

<400> 692

ccgcactngt aangnccgcc agngngctgn aantccgctn agcncggatc cactagtcca 60
 ttgatggtaa aagggtagct tactggnatg tccgctgct ccanganata atacncagga 120
 cttctcanag cacttaatat gttaatataa aactncgnga aaaaagatnt tcnatgaanc 180
 ntctctctta ggaggtcagg ngagaatagt gttaatgnca ttaagganag aacga 235

<210> 693

<211> 383

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(383)

<223> n = A,T,C or G

<400> 693

nttatgtaag aaatgtcata tatcttttat tttctttaaa tcaaaataaa tatgactttg 60
 agcatcccat cccatgcccc atcctatcag aatggtagga acatcaacac aaataattag 120
 taatgcaccg catctacatt cccatgctct ctttacttct tcagcattgc ctaaaggcat 180
 aatacacctt taattaatta attcagcctc ctaatgcaca ttaacaaagc ccctgctaga 240
 ctctgtccat aatggnaaac ctgnatgatc cttgatatta acantttaag gaatgctcat 300
 ggattggtn cagacttaaa aaattgaggg ggctgaanaa aatctaangg anaaatcatg 360
 gaagcatttg cacatattac ata 383

<210> 694

<211> 204

<212> DNA

<213> Homo sapien

<400> 694

tctcttggct ggtcagcctg aagggtggta atgactcacc aacgctacta atccttcttc 60
 actgtccctt atttttttcc ctcccaggct cataactcga ggttaaactc tcttttatac 120
 agaaccctg tctgatgaag catcatttca gaattttaag tcaacttaca aatgtggtat 180
 tattcacatc tgagtacaaa tttta 204

<210> 695

<211> 670

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aaatgagact	aactaatcaa	tccgaggcaa	ggggcaaatt	agacggaacc	tgactctggg	2460
ctattaagcg	acaactttcc	ctctgttgta	ttttcttttt	attcaatgta	aaaggataaa	2520
aactctctaa	aactaaaaac	aatgtttgtc	aggagttaca	aaccatgacc	aactaattat	2580
ggggaatcat	aaaatatgac	tgtatgagat	cttgatgggt	tacaaagtgt	accactgttt	2640
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aacagaaatt	catttctcac	agttctgggg	gctggaagtc	cacgatcaag	gtgcaggaaa	2820
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gcactgtggg	gtgggggggt	gtggctgctc	tgctctgagt	ggccaagata	aagcaacaga	3060
aaaatgtcca	aagctgtgca	gcaaagacaa	gccaccgaac	agggatctgc	tcatcagtgt	3120
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taaattcaat	gcgcccttgt	atcccttttt	cttttttatac	tgtctacatc	tataatcact	3600
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<210> 699

<211> 2051

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(2051)

<223> n = A,T,C or G

<400> 699

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<213> Homo sapiens

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<213> Homo sapiens

<400> 703

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<211> 4034

<212> DNA

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ttgctcctac ccctaggaca aggggtggac tcctgactct gcagataaat tctacaaaag 840
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ctgtgaggat tgcaggctct ggagtcacac tgcttgttga aacgctgcct cttaccctcc 960
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gaagacgtag cacagtgtcg agtacggaat gttatttcca tccttctcac ggagcttggg 1140
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aggcattggg ccagtgtctg gcctgggtctg tgtcccgctc ctaggctcag ccagtacca 1260
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caggccccgt gagctggcac tgetcatcct gggcggtggg ctgctggact tctgtggcca 1440
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tcgccaggcc tactctgtct atgccttcat gatcagctct gggggctgcc tgggctacct 1560
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ggctgaggag gcagcgctgg gccccaccga gccagcagaa gggctgtcgg cccctcctt 1740
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tccccggctg caccagctgt gctgcgcgat gcccgcacc ctgcgcggc tcttcgtggc 1860
tgagctgtgc agctggatgg cactcatgac cttcacgctg ttttacacgg atttcgtggg 1920

```



```
<210> 706  
<211> 123  
<212> PRT  
<213> Homo sapiens  
  
<400> 706  
Met Gly Ser Leu Gly Leu Phe Leu Gln Cys Ala Ile Ser Leu Val Phe  
          5                      10                      15  
Ser Leu Val Met Asp Arg Leu Val Gln Arg Phe Gly Thr Arg Ala Val  
      20                      25                      30  
Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala Gly Ala Thr Cys  
    35                      40                      45
```

Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala Ala Leu Thr Gly
50 55 60

Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr Leu Ala Ser Leu
65 70 75 80

Tyr His Arg Glu Lys Gln Val Leu Ile Gly Gln Trp Val Glu Ser Gly
85 90 95

Trp Glu Gly Trp Ser Gly Phe Leu Gly Gly Gln Leu Ala Gln Asn Leu
100 105 110

Val Ser Gly Lys Gln Leu Trp Arg Met Leu Leu
115 120

<210> 707

<211> 150

<212> PRT

<213> Homo sapiens

<400> 707

Met Val Gln Arg Leu Trp Val Ser Arg Leu Leu Arg His Arg Lys Ala
5 10 15

Gln Leu Leu Leu Val Asn Leu Leu Thr Phe Gly Leu Glu Val Cys Leu
20 25 30

Ala Ala Gly Ile Thr Tyr Val Pro Pro Leu Leu Leu Glu Val Gly Val
35 40 45

Glu Glu Lys Phe Met Thr Met Val Leu Gly Glu Ser Leu His Pro Pro
50 55 60

Ser Phe Leu Phe Gln Ile His Ala Thr Trp His Val Gly Gln Glu Tyr
65 70 75 80

Leu Cys Pro Gly Ser Cys Leu Glu Gly Glu Val Val Cys Trp Glu Gly
85 90 95

Ile Ala Gly Gln Glu Gly Asp Pro Gly Leu Arg Gly His Thr Lys Arg
100 105 110

Lys Lys Arg Ile Pro Arg Thr Tyr Pro Ser His Leu Trp Ile Pro Gly
115 120 125

Pro Ala Gln Ser Leu Ala His Arg Arg His Trp Arg Asn Ala Pro Asn
130 135 140

Leu Trp Leu Ala Leu Leu
145 150

002230-682990

<210> 708

<211> 371

<212> PRT

<213> Homo sapiens

<400> 708

Met Leu Phe Pro Ser Phe Ser Arg Ser Leu Val Pro Leu Pro Leu Ala
 5 10 15

Leu Tyr Leu Ser Gln Pro Leu Thr His Thr Thr Ser Leu Leu Ala Gly
 20 25 30

Ile Gly Pro Val Leu Gly Leu Val Cys Val Pro Leu Leu Gly Ser Ala
 35 40 45

Ser Asp His Trp Arg Gly Arg Tyr Gly Arg Arg Arg Pro Phe Ile Trp
 50 55 60

Ala Leu Ser Leu Gly Ile Leu Leu Ser Leu Phe Leu Ile Pro Arg Ala
 65 70 75 80

Gly Trp Leu Ala Gly Leu Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu
 85 90 95

Ala Leu Leu Ile Leu Gly Val Gly Leu Leu Asp Phe Cys Gly Gln Val
 100 105 110

Cys Phe Thr Pro Leu Glu Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro
 115 120 125

Asp His Cys Arg Gln Ala Tyr Ser Val Tyr Ala Phe Met Ile Ser Leu
 130 135 140

Gly Gly Cys Leu Gly Tyr Leu Leu Pro Ala Ile Asp Trp Asp Thr Ser
 145 150 155 160

Ala Leu Ala Pro Tyr Leu Gly Thr Gln Glu Glu Cys Leu Phe Gly Leu
 165 170 175

Leu Thr Leu Ile Phe Leu Thr Cys Val Ala Ala Thr Leu Leu Val Ala
 180 185 190

Glu Glu Ala Ala Leu Gly Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala
 195 200 205

Pro Ser Leu Ser Pro His Cys Cys Pro Cys Arg Ala Arg Leu Ala Phe
 210 215 220

Arg Asn Leu Gly Ala Leu Leu Pro Arg Leu His Gln Leu Cys Cys Arg

```
<210> 709
<211> 141
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (1)...(141)
<223> n=A,T,C or G

<400> 709
tacggcgtgg tgcggagggc ggtaccccac aaataacacn nacaccccat cctatctgtg 60
tccacanata aantgaactca ttctctctct cgcatanccc actntcccoct ngcgataaccg 120
taacnaancc ctccccctt t 141
```

<220>

<400> 726
 ttgggtgggt tgggtggggg naaatttncc catttggtg ggtttggggg ggnaaatact 60
 tcccgcttt tnggtnccca aaganacnaa gggggagtcc cttnatagag gnagncgat 120
 ncntcncaac nacntngact ttgnccatgg ggagnaaggt gg 162

<210> 727
 <211> 120
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(120)
 <223> n=A,T,C or G

<400> 727
 gtgtgggtgg ggaattccat tgtggttggg ggnaaatctc cgcttgtcca aagnacaggg 60
 ggggtcncctt anagngnagg gggttcctcc ccaccacttg ncttgnccat tngagnaag 120

<210> 728
 <211> 130
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(130)
 <223> n=A,T,C or G

<400> 728
 gaccactgc agcgttnaac ttagcttgga ccgagctcgg atccctagtc cgtgtggtgg 60
 aattccatgt gtcgagagag gggcaaatac nctccaanac ancncctca tgctcnacac 120
 atattcgcat 130

<210> 729
 <211> 182
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(182)
 <223> n=A,T,C or G

<400> 729
 cngactgctn gcgtttaaac ttaagcnagg taccgaacgg ggatnnacga ctantgatcg 60
 gctggctgct tccagtcgat tanatttggtg aaaaagctga accncngccn gttaaggggg 120
 annatgcaaa anatncatcc nnetgccccn taaactgnct tntccnaggg aaaaaangga 180
 ag 182

<210> 730

<211> 678
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(678)
 <223> n=A,T,C or G

<400> 730
 cactcncact ccggacctag gcncttcacc actgctctct tctcctcct cctcctctc 60
 ctcggggctg ggggaccttc ccagtgacc atctcacttt ggctgaancc cactcggggc 120
 agcctgagtt tggggctctt ggcttctca cctcctcgg cccctcctt ggcccgacc 180
 aggccaaacc ggggcagccg taccttgagc ttgtgtcgg cctctcctc cccctctgcc 240
 acctggtact cggcatggtt gcccccgga tggcgagagc tccacgtcgg gcagtgagaa 300
 gcagaaagta cgctcggccc ctgggggctg ctctcagca ccctcgcccc ccaccctagc 360
 tctggcccc agtgtgggca acttcagcct cagcccaccc tcgctgtgg ccgcctcgcc 420
 cgctgtgcc tctcggctta gccccacgtc caactcaagc tggggcactg tcacggtggg 480
 catcttaaag acaccctcac ccaccagcag ctaccacct gcaacctggg ctccaggcaa 540
 aaaaagggtc acctggggca nctgaacct gtacctgctg tgccctctgc tgaanggaat 600
 gttatctgaa cctgctgccc tgggggtact gccttcccaa aaccgggtca antccacctg 660
 ttggaaggna aatncccc 678

<210> 731
 <211> 135
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(135)
 <223> n=A,T,C or G

<400> 731
 gagatccgac gtcacccccct tccggcgggc caagacgctg caactcccga ggcngcccaa 60
 atatcttttg aagagcgctc ccagcccaac acaatggaat tccaccacac tggnttagtg 120
 gatccgagct aagcc 135

<210> 732
 <211> 660
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(660)
 <223> n=A,T,C or G

<400> 732
 gcttggtacc gagctnggat ccctagtaac ggccgccagt gtgctggaat tcggctttct 60
 tcaatcagnt nacgagctgc atggtctgct aacattgtca taattgctgg catagattac 120

```

tgaataataa gaaaaaaaat tgaagctgcc tatcaagttt tggattatc aaaaacttcc 180
tacaagttaa tttacttcaa ccatgttatt acaaatatct taatgaatac tttagagact 240
ttaattacaa aaaactgaga tagtaaaagc aagtaataaa agctgaaatt acttagctat 300
ttgataatta cataaattat tatgggccat tcaacttttc tagtgtttag tttatacacc 360
aggaagactt tctatttcta ctaacattta taaagtatgc taacctatta tttaaacgca 420
tccactatta ggatttttatg gcctaaaacg tgatacagtt cagtatcttg atgtcaaaac 480
ttttaagca agtagggatt aagttcaagt gaatgtgatt ttctttcttc ccagtagggg 540
cttctgaata actcagnaag gctcacttcc attatcttac tttataaaaa aatgctataa 600
gacagaatgg gccgacgtgg nggctccacc tgtatccacc tttggaggcg agnggcgaat 660

```

<210> 733

<211> 836

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(836)

<223> n=A,T,C or G

<400> 733

```

aattaatgac tttttttccg ccctgccaaag ctagtttgtc taaatataat gtaaagaaat 60
tagctactca ttttctgggc cacgaagggt cctaaaatgg gaagaagtgg agatctgacc 120
ttgttagttc taaatacact aaactgggag tgccatggat ggctttcagg atgtcctgaa 180
tcccctataa ttgtatacaa aatcgtgagt ttttaaaaaa tgggttagag ctattgggtc 240
ctcagagtct caggcatctt agaccccaa aaagggttaag gactactgac ttaaccaatt 300
aggtttgagt ggcattggct ttgaagaaaa gcagaggaaa gatataatct ataattctgg 360
gcaacaaaaa agtggatgtg tgccagcatc ttagagtaga atcctcttaa aaggatagca 420
ctgcatatga actagtaggt ttaaccagt gcataattag gcgaagtagc tcatttttct 480
gttagaattc ttttttattt gggaatgggc aagcttttac agcttttacc ttgccaatga 540
atacctggaa tttaaaaaat ctgttagagg atattgcca taaagttttt tttcctagat 600
catatattca gtaaataatg ttgtagcttt atttcaatcc cccaattcat tgaggggtga 660
aacaatttga atggtttgag tgtagaagct aagttatttc tgtagaggct aagggcattt 720
ataccaanat atgttagact tngngntcct gttaaccatg ctgtanacaa taggaattac 780
tgtatatcca cattttaatt ttaacatctt ctgctttgnt gntggtttga gangga 836

```

<210> 734

<211> 694

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(694)

<223> n=A,T,C or G

<400> 734

```

nagtntatt tncactaaac tngnagtgcc ttggatggct ttcaggatgt cctgaatcct 60
ctataattgt atacaaaatc gtgagttttt aaaaactggg ttagagctat tggttcctca 120
gagtctcagg catcttagac ccccaaaaag gttaaggact actgacttaa ccaattaggt 180
ttgagtggca ttggctttga agaaaagcag aggaaagata tattttataa ttctgggcaa 240

```

```

caaaaaagtg gatgtgtgcc agcatcttag agtagaatcc tcttaaaagg atagcactgc 300
atatgaacta gtaggtttta accagtgcac atttaggcga agtagctcat tttctgttta 360
gaattctttt ttatttgga atgggcaagc ttttacagct tttaccttgc caatgaatac 420
ctggaattta aaaaatcttg ttaggcataat tgcccataaa gttttttttc ctagatcata 480
tattcagtaa atatgtttgt agctttatct caatcccca attcattgag gggtgaaaca 540
atttgaatgg tttgagtgt gaagctaagt ttttctgtga gaggctaagg gcatttatac 600
caagatatgt tagacttgtg gttcctgtta accattgctg tagacaatag gaattactgt 660
atatccacat ttttaatttt aacatcattc tgtc 694

```

<210> 735

<211> 126

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(126)

<223> n=A,T,C or G

<400> 735

```

ncnttgaaac ngggtgacca gacttcaggc ctgtgcgctc aatcgtggag aatctcgtgc 60
cgaattcggc acgagctctc ctctctctct ctctctctct ctctctctct ntctctctct 120
ctctct 126

```

<210> 736

<211> 165

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(165)

<223> n=A,T,C or G

<400> 736

```

cagaagcctt taaaccggtt ngaccagact tcaggcctgt gcgctcaatc gtggagaatc 60
tcgtgccgaa ttcggcacga gtctctctct ctctctctct ctctctctct ctctctctct 120
ctctctctct ctctctctct ctctctctct ctctctctct ctctc 165

```

<210> 737

<211> 125

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(125)

<223> n=A,T,C or G

<400> 737


```

ggnagccctt ttaaccgttt gtccagactt caggcctgtg cgctcaatcg tggagaatct 60
cgtgccgaat tgggcacgag tctctctctc tctctctctc tctctctctc tctctntctc 120
tctct                                           125

```

```

<210> 738
<211> 137
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(137)
<223> n=A,T,C or G

```

```

<400> 738
ggagncnctt gancaggatg accgacttca ggccctgtgcg ctcaatcgtg gagaatctcg 60
tgccgaattc ggcacgagtc tctctctctc tctctctctc tctctctctc tctctctctc 120
tctctctctc tctctctc                                           137

```

```

<210> 739
<211> 970
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(970)
<223> n=A,T,C or G

```

```

<400> 739
aggcctattht aggtgacact atagaacaag tttgtacaaa aaagcaggct ggtaccggctc 60
cggaattcgc ggccgcgtcg acggcccttn gtgccactag ntctttcatt cttccccccc 120
atcaatcagt gaacttttta gcctactcaa agctttgctc caatgcatag gatttatgat 180
tgtggggatt tccagataat ataaatattc aacatgaata ttttaaatta aggcatgaga 240
catttttctt aactgagcat agccatgaac ctctcacgct tgttcctctg tgtcagtttg 300
tancactgaa tacagcagcc ctccataaaag tccaggcagt gcacaggctc tgacatgatg 360
aagtgcagtg ttgctatggg gatthttgcag ctggccaaat agtcactggg tgattttacc 420
cagcaggaga tttttgcaaa aatttctctg gtgagagtga aatcaaactc ctattttgnt 480
tctctctctc aagctgnagt taagatggat taatgagtag ttttagatta attaactctg 540
aagagaaaat gggagaaaag tgaggaaggg tgttggcaga agtcattgct ggaatccttc 600
tgaaggaggat actgacttca cttgcaaaga cnagagacta naagacaatg aagttaaact 660
tggcctgtct ctcatatgat agatgctgag agtcaggntc agggaaattht aattctgtca 720
tacgcatatn ggattatgtg gtcattggat tgttggcact aaccngcctn taatcagnat 780
aagaaaagtg ttttggtaga naaagaaaat tatggcccag aaaaacctgg aanacttgga 840
aaaaatgntn gggggccttg ggtgggtggc tnaaaanacc ccctggggat ntttaaacca 900
aaantgaaga agggaaaaat ntttccctnt nttttntttt tttgccccct tgggatttgg 960
tttnttttcc                                           970

```

```

<210> 740
<211> 739
<212> DNA

```



```

ggaaaaaaat tngnnngggg gccnttttgt tggggggggt tnaaaaaacc ccctnngggg 1080
ttttttaagc ccaaaagggg gggaggggna aaanggtnc cttntttttt ttttnngccc 1140
cccttgggga atggnnttant tcanggggcc c 1171

```

<210> 742

<211> 739

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(739)

<223> n=A,T,C or G

<400> 742

```

gntgtcnaaa aagcaggctg gtaccgggtcc ggaattcgcg gccgcgtcga cggcccttgg 60
tgccactagt tctttcattc ttcccncca tcaatcagt aacttttttag cctactcaaa 120
gctttgctcc aatgcatagg atttatgatt gtggggattt ccagataata taaatattca 180
acatgaatat tttaaattaa ggcattgagac atttttccta actgagcata gccatgaacc 240
tctcacgtct gttcctctgt gncagtttgt agcactgaat acagcagccc tcctaaaagt 300
ccaggcagtg cacaggtctt gacatgatga agtgacgtgt tgctatgggtg attttgcagc 360
tgcccaaata gtcactgggtt gattttaccc agcaggagat ttttgcaaaa atttcctggg 420
tgagagtga atcaaaactcc tattttgttt ctctctgca agctgnagtt aanatggatt 480
aatgagtact ttttagattaa ttaactctga agagaaaatg ggagaaaagn gaggaagggt 540
gttggcagaa gtcattgctg gaatccttct gaaggagta ctgacttcac ttgcaaagac 600
aagagactan aagacaatga agttaaactt ggctgtctn tcatatgata gatgcttgag 660
agtacaggnt cagggaat ttaattctgn catacgcata ttggattatg tgggtcatgg 720
ctttgtttgg cncctaacc 739

```

<210> 743

<211> 610

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(610)

<223> n=A,T,C or G

<400> 743

```

ctgtccttat ttcttttagca aaaatttccc aagagaagaa ttgctgggat aatgcacatt 60
taaatttttg atagacattc ccaaataatta tacctgtttt tgagaccttt aattcctgtt 120
gtcaaattgc cctatatatg gagtaataaaa caggatttaa agaaatgagg actaaaaaaa 180
gattatatat aacccaacat aaaggcaacc tcttaggcgt tgacagaaac tgacaacttt 240
ttatctgtgg gtgcgatcca ttataagtaa cctgagcacc ttattttttc tttttaaact 300
ctaggtagga taccggagggt ccacaaattt ttcataagaa atattttttc tctgccttat 360
gagattttta aaaatattat actgcttcaa ttgcatcaaa agaaatggac cctaatatct 420
atgatgaagg atttggaggtt agaagacctg agtttcaatt ttggcatggc tgtttgtcta 480
gctctngat cttggacagg tcaattgact tggcttaate ttctcatcca tttagnngag 540
acagcaccac tattcacagg actattgn cn gaattaccag acaatagcat agngaaaaat 600
ataangcctt 610

```

<210> 744
 <211> 127
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(127)
 <223> n=A,T,C or G

<400> 744
 ttnacctccc tggaccgggc ccccttccc cgggcggntc ccccgggctg caggaattct 60
 gcacgagga gagagagtn gagagagaga gagagagaga gagagagaga gagananaga 120
 gagagag 127

<210> 745
 <211> 458
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(458)
 <223> n=A,T,C or G

<400> 745
 gatatcccgg gattcgcggc cgcgtcgacg tggcctctag tttgtcctgg tccaaagcag 60
 ggaagctggg ctacgtcctg cccaggtcag ccttaggtta agggctgcct gggggagga 120
 acttcctggg ccttcgggtc tctgtgcaact ggggtggctc ctgtggcca gaatgccctg 180
 gagaagggtc ctactggaag cgaagggtgca gggcagcagg gcctgaggcg caggagctgg 240
 tggaggctcc cagcacaggc cgcgcggcca gtcacatcac tgctgatggg ggggggactt 300
 ggggagtttc ccccagaaat gggagggtctc acagtccccg tgctgcaatg ctgtcgggtgc 360
 actgngncng caatgtgctc atggncactt gctttttctc tgtggccccg gccgatttat 420
 ccagcanngc accctcttc tncctctccg anaaagcc 458

<210> 746
 <211> 893
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(893)
 <223> n=A,T,C or G

<400> 746
 aagcaggctg gtaccgggtc ggaattcgcg gccgcgtcga cgtggggagt tagctctctg 60
 gaccccgctc tagagtaagt catcgataga gcatttgctt gatggggact tccagaaggc 120
 canngaaaagt cctgccgact tcctggggaa gcccatccgc acgtgggggtg aggggtcccca 180
 natggaagca gctgtgtatg cagggagggg gcagaggctg ctgccaatgg gcatgtccct 240

```

tacctgaaag ggccacctct ccaggtgaca tgtcctgggg gagccggggc cgtctgctcc 300
ggccagaggc gctcagctca ggccacacca ggcagggcac ctcccaacct ggacagggtg 360
ggaccaaggt ggccttggac aaaactctct gtgtttgcca agcacccaat cggacacaga 420
gagtcaacca caccctcagtc acatggtgtc cacacngcag ggggtcaagga ggcccggccc 480
ctccccctca gacgtccctg ggctctctgg agtcagcaag gacgaggacg gcattgacct 540
tcgagacagg aagggtgagta cctcctcccg gcggcatcca ggctcngctt ctccggagag 600
gagagggggc tacttgctgg ataaancggc cggggccaca gagaaaaagc aagggtgacca 660
tgagcacctt gcaaacacag tgcaccacc agcatttnag caccnnggac tgtgaagacc 720
tcccatttct tcggggggaa acncgcccac ngttcccccc accntcacta gtgnattgtg 780
acctgggggn cgggcccacc cctgtngctt gggnnagccc tccnccagg tttctnnggc 840
ngcccnttaa nggnccctng nttggccctt tggcncctt tncgcttttc cca 893

```

<210> 747

<211> 738

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1) ... (738)

<223> n=A,T,C or G

<400> 747

```

gatatcccg gaattcgcg cgcgctcnac gaagcacaga cctgngccct gctctcatgg 60
ggcagactgc catttgtcat tnattactga aggaaagga tcctcagttt gcttgtggac 120
atttcaaatt tgaggtgaga gttggataag taagaataaa gctgctcttc aaagagatga 180
atatagaaaa agaaacaaga tacagncttg gcagtaaggc tgggaggaag gggaaaaggt 240
aataaagaat gaaagagtga gaaatgtgag caggagctga acacagaaaa gttcagngac 300
agaagcanaa ggagggaaga agggaggagg gtccctttca cagaggctca cgaggatgct 360
ttatgngtgc catgcagtcc atgttcagga tgtctgcttc ttanctctct acttttctaa 420
tanaaatttg gatacttact gatcctacat atgtaacagg gagagaaggt gaatttcaaa 480
gcantaaatt gaaaaattgt tcacaatttc atttttttaa aaaagggagc taacagaaga 540
agaggttaat gtggttaatta taggatgnct cttgcgacac atgaatgnat ctgggtatcat 600
ctgagtggga ggggagctgt cttoctgacc caaaaggatc ctttcgttan ccngnactta 660
ngtcccaaaa cctcaccacc ttggagaaat natttccttt tgggggtntc attaaancct 720
tttgncccc gcaaaagc 738

```

<210> 748

<211> 647

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1) ... (647)

<223> n=A,T,C or G

<400> 748

```

ctntgtggcg gtggctgtct catttgggtg gacttttttg gtcgtaggaa cctggtatng 60
aggctcgagag taagacgggc tattagtagt cgcacggag ttatttgtga aaacctggtt 120
agggcctctg tctccgctgc gctcgcctaa attggtatgg ctcgacttgg aaacacggtt 180

```

```

ctaacacgcg ttgttagcgc ccttgctagc atgtgaagga cactggccct accaagaaag 240
attcgagtcg ctccctcccg tatcgttcac ggaggcgata ttactcttc ttactacggg 300
tacttcgaga ttgtctgtga agtttaagac tactaaaaag agtattaagc ctatcgggaa 360
ttagctagat cgacacgcta aaaccaaggg caatcggcgg aaatatagag gcaccaataa 420
tagggcctac agaaggcccg agggttagac tcacgtttta taccggccac gggagaaata 480
aaaagataaa gtatacatcg tttagcggtc ctcggaagcc ttcggcttta atgccaaagga 540
gtcgggaagca tcgtcggcga gtaataaaact ccatcgcgcc gagactatct acgacgcctt 600
ccttaanatc cgtaaattac tcccggaaag agtatttagg cggtctct 647

```

<210> 749

<211> 642

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(642)

<223> n=A,T,C or G

<400> 749

```

ctntgtggcg gtggntgtct catttgggtg gactttttgg gtcgtaggaa cctgggatgc 60
aggtccgcgg agcgtgggct ctcgtcgtgg atgttggggg ttggtgtggt gccggttggt 120
tttggttctg ttgagcgtag tgtgtttgaa ggtagcgtt cgtgtcttgc ttgtggtttg 180
gtgttttagg cggttgggga gggtgtgtg tagctgttgt atgtcatatt gttggtgttg 240
ctgccctgtg ctgtttgtcc ttggttattg tggttgttac ccgcctgtg tggaagtgtt 300
gtggcagggc gggaatttaa gtgggagagt tgtgggacct gtggttgttg ttacgttgct 360
gcttttgtcg tgggcggtgg cggcgcgtct gataattaga attggatacg gagtgtataa 420
tacttctagt aaatggggac ctagtgcctg acttcccggg atagggatct atgcgaagtc 480
cttaggatag tctttgataa gtttaacgcc cagcaccta aaattataca cgattagacg 540
cataacgact cctccaggaa agataaagaa tctcacatat agaacgggac ccatacacg 600
tcggatagga aacaagagaa ctaattttng ttaaaaagac tt 642

```

<210> 750

<211> 639

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(639)

<223> n=A,T,C or G

<400> 750

```

tttgtggcgg tgggtgtctca tttgggtgga tttttgggtc gtaggtaacc tggatatngag 60
gtatagatgc cgattggtcc cgacgagcgt cagcataaat tcggtagttt cgcccttttt 120
agaaggcgct agtactcgga acttcacttc atctcggtag tttacttttg cgtatatagc 180
cttctccctc gaagactagc cgtcacattc gttccctagg aatcgtttct gccctaaga 240
atccgagagc gagatcccgga aactagagga accttagaag agtcgtatct ccacaaggac 300
cccacagtca ttccgggaaa atccctagga ccatacgggt aggattcccc cggaaccggy 360
agcaaaagctc atgatttccc acaccgcgag agcgccata accctatccc atttcttcgy 420
gttatcgagg atattacgat caagccgaga gaaccgctag aaccgctttc ttcgctttct 480

```

```

cacggaacct ataagtagaa agagaaactc aggtcttaag ggggcgcttc ggctaacgaa 540
acttctactt acgaagagag tatctagaca ttaagtcata aaaatccact acgcacctcg 600
tgtacgatat catcgggagc ggttcataga cgggtgtccg 639

```

<210> 751

<211> 637

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(637)

<223> n=A,T,C or G

<400> 751

```

cttttgtggc gnggtgtct catttgggtg gatttttggg tcgtaggnaa cctggtatng 60
aggcagctct gagccccccc ccccccccc cccccnccc ccccccccta gnggttggg 120
aanacggtgg atacctaaat cgagtgngtt cattaaaagt agttgattac nccctaaaat 180
aanaanaggg cttcgtcggg anaaatcggg aagganaagt ctttntggca tcataanaat 240
actggctcgg gtcctaanat ntttaaggng gtcnccgagg gtnttcatac cgataanaaa 300
cgttttccta tcggcaacgg gcttacctga gggnggactt ctncggngc ggngattnan 360
acgaanacgt agaggattnc cgntacttnt tganatcacn cgtatcatac ttgtaagcat 420
aatnttcctg aaaagtgtta taanaatacg cncgcataatt cgcttttttcg tcctagggat 480
gcttaaatgg cgatactgct atagcgggtg agcgttgggt ctcgagnaana aaagcgtgtc 540
ctaattgcgtc taaggnttta aggncgttgg tttaaaaata nccttagaaa cctcgaggcg 600
gatactgggt tntttttaac gaaacaaagc accccnn 637

```

<210> 752

<211> 644

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(644)

<223> n=A,T,C or G

<400> 752

```

tntgtggcgg tgggtgctcat ttgggtggat ttttgggtcg taggaacctg gtatgaggtc 60
ttgcgagttg ttggtgtgtc ctgctgttcg gtggttccct tttgagttga gtttgtcctt 120
tgaggttggt agctgctgtt cgtttgtgtt cgtgtagtgc tttgggttga gaggttatg 180
gtggtggtta cgggtgtattg tcgcccgtgg tcgcgggggt ggggtgggtc tcggttttgt 240
ggttcatagt agtcttctgc gttcgggtgg gcgggttttg gtgagtagtt tcgttcttgg 300
atgtcccat gacccgccat aatctaagta agggttagta gaaacctct cccgatagac 360
acaaccgtcg tccactaaag acctcgctc tgatttttaa aaggaccgga aaaacatccc 420
ttcaacggaa aaaacggaaa aaaagtcagc gaattcaaag aagccacggg agagaaaaaa 480
gaactaaagt tagtccgtca ttatatgtct ctcggagga ggaagcggcg gtggcggaaa 540
atgaggcggg aagaaagacg acctctatcg gcggcttang ccctaaaagg gcgatacctt 600
acgggatgat aaggacccta ggacgcctcc ttctcggatc gtcc 644

```

<210> 753

<220>
 <221> misc_feature
 <222> (1)...(721)
 <223> n=A,T,C or G

<400> 755
 accggattng ttncctgagcg cgtgactgct aataaaaaag atggantgcc atctttttttt 60
 ttnccttgct ttatatatcc agcagcaaaa caaaattggt ctgcngggct ataaaatttg 120
 gcttgtagt cntgtacaca actcaggagt gtgacacagc taccagcttt cctcctaact 180
 ctcaaggga gaaaattcaa gttctgtcta ggctcactct gtaaagtggg aaacttgctg 240
 gttttgtagg ctttttttcc ctttctttcc ctctctcagc ttctccctgc ttctcagaan 300
 atggagttgt gatgcctgca acttaccaaa tttatctatg aatcagattc cagtgggaga 360
 cccctaaagc agaggagaa taaggagttc tccccatgat ggaaaatatc caaagacaag 420
 gtttcattga gcaaagaatt ctggctagat ttggtttgta agtggatccc tccccactgc 480
 gtgtacactt tatctgtctc ttgtcttctt cccaccctc ttctccagct ctctctctgt 540
 ctctctcttg ntccctgac ctttttttct tccantgca tacttttttn ttccctttt 600
 ttaatcttct atantcttaa ncctaccaan gggccctcnt gannaatttn tcaccctga 660
 ataggggatt cntangccc tgagaatttc nttatcanaa aaatattttt ttaaagcatt 720
 a 721

<210> 756
 <211> 873
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(873)
 <223> n=A,T,C or G

<400> 756
 ggaagaatac agtaagtttg caaattaaaa tttctctatt tttctgttat ttattcattt 60
 ggaaactgtc agcctgtctc ttctactttg ggcaagtga agcaaagacg tccagtccta 120
 tcagcaatta ggctgaaagt caacgccaag ctggcgggca agggctgggc tgagtagagg 180
 ttccctaggc aggcaagaga gagactccca ctcgatactc ccagctcggc aactgcctga 240
 atgccaatga gcaactcatta taaccgcgcc tattttatag gatttaattt tacacttcag 300
 gcttaatcag tctgaaagt aaactgacag tgttaagtta cggaatcaat gacatttagg 360
 ctttatgact ttgtagctga atatctatgg gctatatctc cattctaaca gtgatattct 420
 gttccagaat ctcatctctt ggtgatggca ctttctagtg gagcagtcac ggtaacagtc 480
 cacaccatt accatgtggg tgctttacag catactgacg gaaggactga ggagccaccg 540
 gagcaggagt tcctctcagg gaggaagctg acacttccac agctgcctan gtatgggcac 600
 ctgatgccaa cgaanaaccc aaagcgctct cccttccaga tggaagctgc cccactactg 660
 gctgacagca tctggagctg ctctggtcca aatcccgaa tcgcacanct cctancgggg 720
 gcgtttanag atcctcnggg ccagctaccg accacttttg acaaggggnc taggagcgat 780
 aactagnctg gcgcgttaca cncggatgga acgtcttgga cttgagacct cttgggggan 840
 atggcncccc caaataantt gggaaaaantn ggg 873

<210> 757
 <211> 782
 <212> DNA

<220>
 <221> misc_feature
 <222> (1)...(657)
 <223> n=A,T,C or G

<400> 759
 ctttgtggcg gtggtgtctc atttgggtgg actttttggg tcgtaggaac ctggtatnga 60
 gggctctata gaaagcctct tgtctttaga tacgggcttt ctggtccttc gttctggaag 120
 tgtagtagta ggtactgcgg gaaggcgaag agtcctttca aggacgattt acttaagttg 180
 gcttattcta tagttccttc gggacataag gtcggtacga tctatactgc gtgggaagct 240
 gataggttgg gacttaaggc gaataagaag gaggcggcgg aggtcgcgat taccgcagag 300
 atattattta cggcggccgc gggtagccgc ggtcatgcgg aaattttctg aggttcttgg 360
 attcctaaga tcgctcccgt cgagtatact agcgacgaac gtaagagtgc cctcacaaga 420
 accggtacaa actcaagaag aagttcccat taagcatcgt aagaaacggg aggacgagga 480
 cggtaagaag taatcggaga aaggatccta gtngttacga agaagcatcg ttnagctact 540
 ttgcgctacc gtttatattt agacgtgttc cgtccttctc cgtgtttana aaaaagggtt 600
 attccgacgg gagacttagg cgaatggagg gttccgcggg tganaatcgg ancgggg 657

<210> 760
 <211> 644
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(644)
 <223> n=A,T,C or G

<400> 760
 ctttgtggcg gtggtgtctc atttgggtgg actttttggg tcgtaggaac ctggtatgna 60
 ggaaaagaag taagcctcga agcctatctc cgaccgtatt tatttcgcag aagacggaac 120
 tacggacgtc gttaaccccc agtagcccc gtaagaaagg actaaagcga atggaaaagt 180
 cgggaattcc ggcggagggg cggcgattac tgaaaggagt aagagtaaga ctattgcat 240
 acttgaggcg ttccctctta aaaggcaccg gaaacactct attaaaaaac acccgaagaa 300
 gaacaactca tgcgatcggc cgtgtgcagc cgtcaatagt aaagagagcc atgaaccatg 360
 ccatccttag accaattagg atgaagaaga ggaggaagat gaggaccaa cctaccac 420
 tcggaaaacc ccgcacgagc ctccgaacaa aatccgggaa ttaaaacggc ggcccacttc 480
 cgcactctcg tagcgcggac cgaatagaaa accggaaact acagctaaag ggtcctttcc 540
 ggctgttat ctaccacccc gcaatccgat cctccccccc cctcgtccaa aaaccctaac 600
 ctctgcggca acattagagc agaaggagag ggcgatccct tgan 644

<210> 761
 <211> 647
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(647)
 <223> n=A,T,C or G

<400> 769

```

aaagctggag ctccccgcgg tggcgggcgc tctagaacta gtggatccac tagtccanng 60
ngggggaatt cgcggccgcg tcgacctcta tacctttgnt catgcagctt cctctgactg 120
ggtttgttct tcacttggct aacccctctt ttacttaagc acaccttgaa cattccctcc 180
ttccccattt ccccgagng cccctaattg acatacttct gaataacaca ggtgggtattc 240
cttccttggt ggaacctcct ggaggaagag acagatgatt aacaaatcct tccatcaacc 300
cctttgacca tgacatcaac agtgctcaa attatgggt accgtattag cctatgtcta 360
tcttgatcag aatccttacc tcggtgtatt gaaattatct atttcgtgcc tgccctcttta 420
aagtcagggg ttgccttacc tattgtctaa caccatgcag taggtaacat gcagtaggaa 480
acatggcatt aaattatttg ggttcaaata ccagttatgg tgtgtaaata cctaccaggc 540
cgtgaggcac ctgctaagca ggttgacgc atcatttgaa ttcacaccac ccttttgcaa 600
tagaacagat aggcaacaga ggctcatttg ggctaaagga tttgatggag gggaagtgcc 660
aggattccca ccaaggcctc anggccagg tccanggacc atgtctgttg tgacaactgg 720
agtgcatctc atatccctn ctctgngggg naaggtecc cncgnggaga acnnttaaaa 780
caatcatntc tngggggnnt aatgcttctt nccccagtgt ggtncactgc ngccacgagt 840
ccanccact agtcccangt ctgtcatgaa ccanccc 877

```

<210> 770

<211> 874

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(874)

<223> n=A,T,C or G

<400> 770

```

ctggnctccc cgcggtggcg gccgctctag aactagtgga tccactagtc cagtgtgggtg 60
gaattcgcgg cgcgctcgac cttttcaaag gttaacttat ttaattatca cannngcaac 120
ccgatgagta ggtaacagta ttttactgat aggtaatcta aagaaggagg ctaaataaat 180
tgcccaattt cgaacagtga gaggaagaat taggattgaa acacatatag tggcttcaga 240
atctgtaacc ctcacgatgc cactactact tctttcagaa taccctttgc ctatctattc 300
tgttcctatg tcatcaaatt atacttactt taaaaagtat ttgtctttat tattttttaa 360
aaaacacagg gaagtatttc tgatcagggg cagtattggt tctgaaagac aagccagtgt 420
ttttgagggg ttctcccttg ccagtttttc tatgctgggt tattcaagtc ctaagaattg 480
tgtagctatt acagaaccgc tttagcaaat gtgttccatt aatcaagggt atttataaca 540
aaatttcac ccaagtttgga gtgctctgaa aacatagcca aaatgttcgc agggctctacc 600
cctctcgtgt gtcccttttt tttagctatt tcagaagcac actggtgcaa tattttacga 660
aatgagtttc ttccccttac ctctgcatcc tctaagaaaa aatcattgnt gttttatgaa 720
natgaanatc ctgctatttc atatcttgat tggagctgct taattaaatg accatttttna 780
aatttgtttt gattccnngc aaaaaaagtt tnttnttgga tgtagggggc tcnnaaagnc 840
caaaaccccc caaaattttt nnttggaac ccna 874

```

<210> 771

<211> 156

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(156)

<223> n=A,T,C or G

<400> 771

```
ttaaaaaanct ggncctccccg cggtggcgccg cgctctagaa ctagtggatc cactagtcca 60
gtgtgggtgga attcgcggcc gcgtcgaccg cgagcggtcg cccttttttt tttttttttn 120
ngtttttttg aanaattcat tgggtattta ttattc 156
```

<210> 772

<211> 586

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(586)

<223> n=A,T,C or G

<400> 772

```
ncaanctggn ctccaccgcy gtggcgcccg ctctagacta gtggatccac tagtccagt 60
tgggtggaatt cgcggccgcy tcgatacaca agtgcacaca agtcnngnat ttattttatc 120
tccagatatg aaacttacc ccagctatgg tcttctatct gttattttaat ttctaggcca 180
atTTTTTcca cttgaatgtc agtattttta ttcaaagtca ccttgtccaa ataccaagtc 240
atcaacttac cctcaaatta tatcctcatt cagaaaatct acatctatta atggtagcta 300
ttttatccct gccccctgct ttttcttttt atattttaatt aatttgntca tccagcaaat 360
gcttattgag caggatttgt aggctaaaca attctanact ttaaggggac acagnttgca 420
aaacaaaatc ctgccttgna tggatactta tgnnatggng ggatacagac aatcaacata 480
atgangngca tcatatataa tggttagnan aatgataagg gnttttgga aaaaaatgca 540
ccanccaan anggattggg aagtggangg ganggtcang ggangg 586
```

<210> 773

<211> 2983

<212> DNA

<213> Homo sapiens

<400> 773

```
agagatagag tcttccctgg cattgcagga gagaatctga agggatgatg gatgcatcaa 60
aagagctgca agttctccac attgacttct tgaatcagga caacgccgtt tctcaccaca 120
catgggagtt ccaaacgagc agtcctgtgt tccggcgagg acagggtgtt cacctgcygc 180
tggtgctgaa ccagccccta caatcctacc accaactgaa actggaattc agcacagggc 240
cgaatcctag catcgccaaa cacaccctgg tggtgctcga cccgaggacg ccctcagacc 300
actacaactg gcaggcaacc cttcaaaatg agtctggcaa agaggtcaca gtggctgtca 360
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tccttaagtc tgaagaaaac atcctatacc ttctcttcaa cccatgggtg aaagaggaca 480
tggttttcat gcctgatgag gacgagcgca aagagtacat cctcaatgac acgggctgcc 540
attacgtggg ggctgccaga agtatcaaat gcaaaccttg gaactttggc cagtttgaga 600
aaaatgtcct ggactgctgc atttccctgc tgactgagag ctccctcaag cccacagata 660
ggagggaccc cgtgctgggtg tgcagggcca tgtgtgctat gatgagcttt gagaaaggcc 720
agggcggtgt cattgggaat tggactgggg actatgaagg tggcacagcc ccatacaagt 780
ggacaggcag tgccccgata ctgcagcagt actacaacac gaagcaggct gtgtgctttg 840
```



```

gccagtgtg ggtgtttgct gggatcctga ctacagtgt gagagcgttg ggcattcccag 900
cacgcagtgt gacaggcttc gattcagctc acgacacaga aaggaacctc acgggtggaca 960
cctatgtgaa tgagaatggc aagaaaatca ccagtatgac ccacgactct gtctggaatt 1020
tccatgtgtg gacggatgcc tggatgaagc gaccggatct gcccaagggc tacgacggct 1080
ggcaggctgt ggacgcaacg ccgaggagc gaagccaggg tgtcttctgc tgtggggccat 1140
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tctcagaagt gaatggtgac aggctcatct ggttgggtgaa gatggtgaat gggcaggagg 1260
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tgggccaaga caggcggaga gatatacct atgagtacaa gtatccagaa ggctcctctg 1380
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gacctgtaaa agagaacttt cttcacatgt cggtaacaatc agatgatgtg ctgctgggaa 1500
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tcttgggctc ctttgaacta cagtgtgaca ctggcaagaa gatggcaaaa ctgtgtgacc 1620
tcaataagac ctgcagatc caaggtaag tatcagaagt gactctgacc ttggactcca 1680
agacctacat caacagcctg gctatattag atgatgagcc agttatcaga ggtttcatca 1740
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accctgagtt ctctatagag ttgcctaaca caggcagaat tggccagcta cttgtctgca 1860
attgtatctt caagaatacc ctggccatcc ctttgactga cgtcaagttc tctttggaaa 1920
gcctgggcat ctctcacta cagacctctg accatgggac ggtgcagcct ggtgagacca 1980
tccaatccca aataaaatgc acccaataa aaactggacc caagaaattt atcgtcaagt 2040
taagttccaa acaagtgaag gagattaatg ctcagaagat tgttctcatc accaagtagc 2100
cttgtctgat gctgtggagc cttagttgag atttcagcat tctctacctt gtgcttagct 2160
ttcagattat ggtgatttaa atttgatgac ttatatgagg gcagattcaa gagccagcag 2220
gtcaaaaagg ccaacacaac cataagcagc cagaccacaa aggccaggtc ctgtgctatc 2280
acagggtcac ctcttttaca gttagaaaca ccagccgagg ccacagaatc ccatcccttt 2340
cctgagtcac ggccctcaaaa atcagggcca ccattgtctc aattcaaata catagatttc 2400
gaagccacag agtctctccc tggagcagca gactatgggc agccagtgct tggcacctgc 2460
tgacgacctc tgagaagctg ccatactctc aggccatggg ttcaccagcc ctgaaggcac 2520
ctgtcaactg gactgctctc tcagcactgg gatgggcctg atagaagtgc attctcctcc 2580
tattgctctc attctcctct ctctatccct gaaatccagg aagtcctctc cctggtgctc 2640
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<210> 774

<211> 3064

<212> DNA

<213> Homo sapiens

<400> 774

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<211> 684

<212> PRT

<213> Homo sapiens

<400> 775

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Leu Pro Asn Thr Gly Arg Ile Gly Gln Leu Leu Val Cys Asn Cys Ile
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Phe Lys Asn Thr Leu Ala Ile Pro Leu Thr Asp Val Lys Phe Ser Leu
 610 615 620

Glu Ser Leu Gly Ile Ser Ser Leu Gln Thr Ser Asp His Gly Thr Val
 625 630 635 640

Gln Pro Gly Glu Thr Ile Gln Ser Gln Ile Lys Cys Thr Pro Ile Lys
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Thr Gly Pro Lys Lys Phe Ile Val Lys Leu Ser Ser Lys Gln Val Lys
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Glu Ile Asn Ala Gln Lys Ile Val Leu Ile Thr Lys
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<210> 776

<211> 679

<212> PRT

<213> Homo sapiens

<400> 776

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Asn Gln Pro Leu Gln Ser Tyr His Gln Leu Lys Leu Glu Phe Ser Thr
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Gly Pro Asn Pro Ser Ile Ala Lys His Thr Leu Val Val Leu Asp Pro
 65 70 75 80

Arg Thr Pro Ser Asp His Tyr Asn Trp Gln Ala Thr Leu Gln Asn Glu
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Gly Asp Ile Phe Ile Val Tyr Asp Thr Arg Phe Val Phe Ser Glu Val
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 Asn Gly Asp Arg Leu Ile Trp Leu Val Lys Met Val Asn Gly Gln Glu
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 Glu Leu His Val Ile Ser Met Glu Thr Thr Ser Ile Gly Lys Asn Ile
 405 410 415
 Ser Thr Lys Ala Val Gly Gln Asp Arg Arg Arg Asp Ile Thr Tyr Glu
 420 425 430
 Tyr Lys Tyr Pro Glu Gly Ser Ser Glu Glu Arg Gln Val Met Asp His
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 Ala Phe Leu Leu Leu Ser Ser Glu Arg Glu His Arg Gln Pro Val Lys
 450 455 460
 Glu Asn Phe Leu His Met Ser Val Gln Ser Asp Asp Val Leu Leu Gly
 465 470 475 480
 Asn Ser Val Asn Phe Thr Val Ile Leu Lys Arg Lys Thr Ala Ala Leu
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 Gln Asn Val Asn Ile Leu Gly Ser Phe Glu Leu Gln Leu Tyr Thr Gly
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 Lys Lys Met Ala Lys Leu Cys Asp Leu Asn Lys Thr Ser Gln Ile Gln
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 Gly Gln Val Ser Glu Val Thr Leu Thr Leu Asp Ser Lys Thr Tyr Ile
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 Thr Ser Asn Gln Tyr Pro Glu Phe Ser Ile Glu Leu Pro Asn Thr Gly
 580 585 590
 Arg Ile Gly Gln Leu Leu Val Cys Asn Cys Ile Phe Lys Asn Thr Leu
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 Ala Ile Pro Leu Thr Asp Val Lys Phe Ser Leu Glu Ser Leu Gly Ile
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 Ser Ser Leu Gln Thr Ser Asp His Gly Thr Val Gln Pro Gly Glu Thr
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Lys Ile Val Leu Ile Thr Lys
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<400> 777

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<210> 778

<211> 1095

<212> PRT

<213> Homo sapiens

<400> 778

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Thr Lys Asp Ser Lys Ala Thr Glu Asn Val Cys Lys Cys Gly Tyr Ala
      50                      55                      60

Gln Ser Gln His Met Glu Gly Thr Gln Ile Asn Gln Ser Glu Lys Trp
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Asn Tyr Lys Lys His Thr Lys Glu Phe Pro Thr Asp Ala Phe Gly Asp
      85                      90                      95

Ile Gln Phe Glu Thr Leu Gly Lys Lys Gly Lys Tyr Ile Arg Leu Ser
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Cys Asp Thr Asp Ala Glu Ile Leu Tyr Glu Leu Leu Thr Gln His Trp
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His Leu Lys Thr Pro Asn Leu Val Ile Ser Val Thr Gly Gly Ala Lys
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Asn Phe Ala Leu Lys Pro Arg Met Arg Lys Ile Phe Ser Arg Leu Ile
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Tyr Ile Ala Gln Ser Lys Gly Ala Trp Ile Leu Thr Gly Gly Thr His
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Tyr Gly Leu Thr Lys Tyr Ile Gly Glu Val Val Arg Asp Asn Thr Ile

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Lys 705	Lys	Pro	Val	Asp	Lys	His	Lys	Lys	Leu	Leu	Trp	Tyr	Tyr	Val	Ala 720
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<211> 1095

<212> PRT

<213> Homo sapiens

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Lys	Ala	Ile	Asn	Thr	Ser	Ile	Lys	Asn	Lys	Ile	Pro	Cys	Val	Val	Val	
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Tyr	Ala	Leu	Tyr	Lys	Ala	Phe	Ser	Thr	Ser	Glu	Gln	Asp	Lys	Asp	Asn	
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Trp	Asn	Gly	Gln	Leu	Lys	Leu	Leu	Leu	Glu	Trp	Asn	Gln	Leu	Asp	Leu	
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Val	Arg	Leu	Phe	Leu	Glu	Asn	Gly	Leu	Asn	Leu	Arg	Lys	Phe	Leu	Thr	
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His	Asp	Val	Leu	Thr	Glu	Leu	Phe	Ser	Asn	His	Phe	Ser	Thr	Leu	Val	
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Glu	Asp	Arg	Asn	Gly	Arg	Asp	Glu	Met	Asp	Ile	Glu	Leu	His	Asp	Val	
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Gly Cys Thr Leu Ala Ala Leu Gly Ala Ser Lys Leu Leu Lys Thr Leu						
		580		585		590
Ala Lys Val Lys Asn Asp Ile Asn Ala Ala Gly Glu Ser Glu Glu Leu						
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Ala Asn Glu Tyr Glu Thr Arg Ala Val Glu Leu Phe Thr Glu Cys Tyr						
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Ser Ser Asp Glu Asp Leu Ala Glu Gln Leu Leu Val Tyr Ser Cys Glu						
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Ala Trp Gly Gly Ser Asn Cys Leu Glu Leu Ala Val Glu Ala Thr Asp						
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Gln His Phe Ile Ala Gln Pro Gly Val Gln Asn Phe Leu Ser Lys Gln						
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Trp Tyr Gly Glu Ile Ser Arg Asp Thr Lys Asn Trp Lys Ile Ile Leu						
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Ser Val Pro His Pro Pro Glu Leu Val Leu Tyr Ser Leu Val Phe Val						
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Phe Thr Asp Leu Trp Asn Val Met Asp Thr Leu Gly Leu Phe Tyr Phe						
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						800
Ile Ala Gly Ile Val Phe Arg Leu His Ser Ser Asn Lys Ser Ser Leu						
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Tyr Ser Gly Arg Val Ile Phe Cys Leu Asp Tyr Ile Ile Phe Thr Leu						

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Arg Gln Asn Glu Gln Arg Trp Arg Trp Ile Phe Arg Ser Val Ile Tyr		
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Glu Pro Tyr Leu Ala Met Phe Gly Gln Val Pro Ser Asp Val Asp Gly		
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Thr Thr Tyr Asp Phe Ala His Cys Thr Phe Thr Gly Asn Glu Ser Lys		
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Pro Leu Cys Val Glu Leu Asp Glu His Asn Leu Pro Arg Phe Pro Glu		
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	980	990
Val Gln Glu Tyr Cys Ser Arg Leu Asn Ile Pro Phe Pro Phe Ile Val		
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Phe Ala Tyr Phe Tyr Met Val Val Lys Lys Cys Phe Lys Cys Cys Cys		
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Lys Glu Lys Asn Met Glu Ser Ser Val Cys Cys Phe Lys Asn Glu Asp		
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Asn Glu Thr Leu Ala Trp Glu Gly Val Met Lys Glu Asn Tyr Leu Val		
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Lys Ile Asn Thr Lys Ala Asn Asp Thr Ser Glu Glu Met Arg His Arg		
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1095

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 Val Arg Leu Phe Leu Glu Asn Gly Leu Asn Leu Arg Lys Phe Leu Thr
 465 470 475 480
 His Asp Val Leu Thr Glu Leu Phe Ser Asn His Phe Ser Thr Leu Val
 485 490 495
 Tyr Arg Asn Leu Gln Ile Ala Lys Asn Ser Tyr Asn Asp Ala Leu Leu
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 Thr Phe Val Trp Lys Leu Val Ala Asn Phe Arg Arg Gly Phe Arg Lys
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 Gly Cys Thr Leu Ala Ala Leu Gly Ala Ser Lys Leu Leu Lys Thr Leu
 580 585 590
 Ala Lys Val Lys Asn Asp Ile Asn Ala Ala Gly Glu Ser Glu Glu Leu
 595 600 605
 Ala Asn Glu Tyr Glu Thr Arg Ala Val Glu Leu Phe Thr Glu Cys Tyr
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<211> 132

<212> PRT

<213> Homo sapien

<400> 819

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35     40     45
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50     55     60
Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr Gly Asp Val
65     70     75     80
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85     90     95
Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser Val Asn Trp
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<223> PCR primer

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<211> 358

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Leu Pro Ser Asp Gly Lys Lys Met Val His Val Gln Asp Phe Thr Ala
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Phe Trp Asp Lys Ala Ser Glu Thr Pro Thr Leu Gln Gly Leu Ser Phe
 50 55 60

Thr Val Arg Pro Gly Glu Leu Leu Ala Val Val Gly Pro Val Gly Ala
 65 70 75 80

Gly Lys Ser Ser Leu Leu Ser Ala Val Leu Gly Glu Leu Ala Pro Ser
 85 90 95

His Gly Leu Val Ser Val His Gly Arg Ile Ala Tyr Val Ser Gln Gln
 100 105 110

Pro Trp Val Phe Ser Gly Thr Leu Arg Ser Asn Ile Leu Phe Gly Lys
 115 120 125

Lys Tyr Glu Lys Glu Arg Tyr Glu Lys Val Ile Lys Ala Cys Ala Leu
 130 135 140

Lys Lys Asp Leu Gln Leu Leu Glu Asp Gly Asp Leu Thr Val Ile Gly
 145 150 155 160

Asp Arg Gly Thr Thr Leu Ser Gly Gly Gln Lys Ala Arg Val Asn Leu
 165 170 175

Ala Arg Ala Val Tyr Gln Asp Ala Asp Ile Tyr Leu Leu Asp Asp Pro
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Leu Ser Ala Val Asp Ala Glu Val Ser Arg His Leu Phe Glu Leu Cys
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210
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Asp Phe Gly Ser Leu Leu Lys Lys Asp Asn Glu Glu Ser Glu Gln Pro
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Pro Val Pro Gly Thr Pro Thr Leu Arg Asn Arg Thr Phe Ser Glu Ser
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Ser Val Trp Ser Gln Gln Ser Ser Arg Pro Ser Leu Lys Asp Gly Ala
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Asn Arg Ser Glu Gly Lys Val Gly Phe Gln Ala Tyr Lys Asn Tyr Phe
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His His His His His
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Lys Glu Ser Leu Phe Tyr Lys Met Val Gln Gln Leu Gly Lys Ala Glu
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Ile Ala Gly Gln Ile Lys Leu Pro Thr Val His Ile Gly Pro Thr Ala
      35                      40                      45

Phe Leu Gly Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val
      50                      55                      60

Gln Arg Val Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr
      65                      70                      75                      80

Gly Asp Val Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr
      85                      90                      95

Ala Met Ala Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser
      100                     105                     110

Val Thr Trp Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr
      115                     120                     125

Leu Ala Glu Gly Pro Pro Ala Glu Phe Met His Gly Pro Gln Val Leu
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Ala Arg Cys Ser Glu Cys Ala Cys Pro Ala Leu Ala Ala Thr Ser Ala
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Gly Val Arg Leu Glu Gly Val Asp Arg Pro Pro Thr Leu Pro Ser Gln
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Gly Ser Gly Trp Pro Cys Ser His Ser Leu Ser Gly Cys His Leu Met
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Ala Asp Gly Ala Lys Ala Leu Gly Lys Ala Asp Gly Pro Trp Pro Tyr
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Leu Phe Val Arg Arg Thr Asp Val Pro Cys Pro Ala Ala Ser Glu Val
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Gly Gly Cys Ala Pro Ser Ser Trp Arg Ala Leu Ala Glu Val Thr Gly
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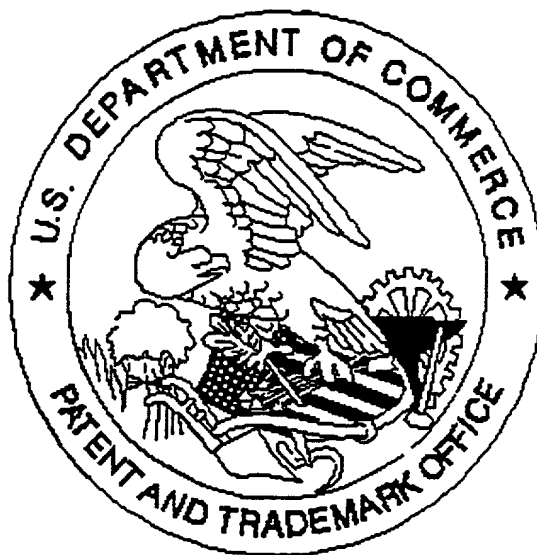
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270

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290 295 300

[illegible]

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for scanning. (Document title)

☐ Page(s) _____ of _____ were not present
for scanning. (Document title)

☒ Scanned copy is best available. *of drawings*

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